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Influence of inspiration level on bronchial lumen measurements with computed tomography

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Summary

Background: Bronchial dimensions measured in CT images generally do not take inspiration level into consideration. However, some studies showed that the bronchial membrane is distensible with airway inflation. Therefore, re-examination of the elasticity of bronchi is needed.

Purpose: To assess the influence of respiration on bronchial lumen area (defined as distensibility) in different segmental bronchi and to explore the correlations between distensibility and both lung function and emphysema severity.

Material and methods: In 44 subjects with COPD related to alpha-1-antitrypsin deficiency (AATD), bronchial lumen area was measured in CT images, acquired at different inspiration levels. Measurements were done at matched locations in one apical and two basal segmental airways (RB1, RB10 and LB10). Airway distensibility was calculated as lumen area difference divided by lung volume difference.

Results: Bronchial lumen area in the lower lobes (RB10 and LB10) correlated positively with FEV_1%predicted ($p = 0.027$ for RB10; and $p = 0.037$ for LB10, respectively). Lumen area is influenced by respiration ($p = 0.006$, $p = 0.045$, and, $p = 0.005$ for RB1, RB10 and LB10, respectively). Airway distensibility was different between upper and lower bronchi ($p < 0.001$), but it was not correlated with lung function.

Conclusion: Lumen area of third generation bronchi is dependent on inspiration level and this distensibility is different between bronchi in the upper and lower lobes. Therefore, changes in lumen area over time should be studied whilst accounting for the lung volume changes, in order to estimate the progression of bronchial disease while excluding the effects of hyperinflation.

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Chronic obstructive pulmonary disease (COPD) is defined by airflow limitation measured by the forced expiratory volume in 1 s (FEV_1),[1] but the limitation may be contributed by different pathologies such as emphysema and small airway disease, both of which can be measured separately with computed tomography (CT).[2] For the assessment of emphysema progression, lung densitometry is a well established sensitive and reproducible method.[3,4] The use of bronchial CT measurements for quantifying small airway diseases is steadily growing in studies dealing with COPD.[5–7]

Airway lumen dimensions obtained from CT lung images appear to be related to FEV_1 more directly than wall thickness. Although lumen area is measured in most studies, the results are not shown or discussed. Instead, wall thickness parameters are used to calculate correlation to lung function.[8,9] Under the assumption that the epithelial perimeter of airways does not change under different lung conditions,[10,11] parameters such as wall thickness and wall area are being used as a measure for airway size. However, studies on distensibility in strips of airway mucosa from guinea pigs[12] and with basement membrane perimeter measurements in human bronchial segments[13] showed that the mucosal bronchial membrane is distensible with airway inflation. Subsequently, Gunst[14] suggested that the utility of wall perimeter as a rigid marker for airway size should be re-examined.

Humans have different lung volumes depending on their height, weight and gender. This influences the size of the bronchi per subject. In addition, subjects show different amounts in volume change between TLC and FRC (dependent on effort and/or disease severity). As a consequence, bronchial CT morphometry may be influenced by lung volume and thus requires a normalization procedure, similar to those in lung densitometry studies,[4,15] in order to estimate progression in bronchial disease while excluding effects of hyperinflation. To study this influence of lung volume we performed bronchial measurements at matched locations in patients who were scanned by CT at different inspiration levels. Subsequently, we examined the distensibility in three segmental bronchi, defined as the response of bronchial lumen to changes in inspiration level, and explored the correlations between distensibility and both lung function and emphysema severity.

Material and methods

Patients

Subjects known with the diagnosis of COPD related to alpha-1-antitrypsin deficiency (AATD) were invited by letter to participate in the Repair study.[16] Forty-four Dutch subjects from this study underwent lung function testing and repeated CT scanning at baseline (untreated). The study was approved by the Ethics Committee of the Leiden University Medical Center and written informed consent was signed by all patients.

Lung function testing

Lung function tests were performed according to the ERS guidelines.[17,18] All tests were performed after nebulization of 5 mg of salbutamol and 500 mg of ipratropium bromide. The following tests were performed: spirometry with measurements of vital capacity (VC), forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC; and single-breath total lung diffusion capacity (carbon monoxide transfer factor – TLco and carbon monoxide diffusing coefficient – Kco).

CT scanning

Within 2 h after airway dilation, patients underwent two subsequent CT scans during the same visit, with a Toshiba Aquilion 16 detector row CT scanner (Toshiba Medical Systems Ltd., Tokyo, Japan), using the following parameters: 135 kVp; 40 mA; rotation time 0.4 s.; collimation: 16×1.0 mm; pitch factor: 1.4375, FOV 329–399 mm, and reconstruction filter FC03. Images were reconstructed with a slice thickness of 5 mm and a slice increment of 2.5 mm. No contrast media were used. Scans were made in supine position during breath hold, and were obtained in caudocranial direction to avoid artefacts due to breathing. The first scan was acquired at total lung capacity (TLC); the second scan was acquired at approximately functional residual capacity (~FRC) level.

Densitometry

Total lung volume and lung density was calculated with the software package Pulmo-CMS (version 1.3, Medis specials, Leiden, The Netherlands). The 15th percentile point (Perc15) and caudocranial locality were chosen as measures of emphysema severity and distribution, respectively.[15]

Bronchial measurements

Three 3rd generation bronchi were selected: the apical segmental bronchus of the right upper lobe (RB1), the posterior basal segmental bronchus of the right lower lobe (RB10), and the posterior basal segmental bronchus of the left lower lobe (LB10).

Within these bronchi, a measurement location was selected using the criteria that the bronchial wall was clearly visible, and that the inner and outer wall contour were approximately concentric. At the selected bronchus locations parallel measurements were performed in paired view in the TLC and corresponding ~FRC image (Fig. 1) using software developed at our institute (BBGui).

To identify the inner wall contour in the CT image, the user manually placed an initial contour within the bronchial lumen. Subsequently, the 2D image was super-sampled using a zoom-factor that was based on the approximate inner contour dimensions. The approximate inner contour was then refined automatically by using dynamic programming to find a closed contour, which follows the local maxima of the intensity gradient (corresponding to the transition from lumen to wall). A similar approach was used to identify the outer wall contour; this contour follows the outer bronchial wall and corresponds to the transition from bronchial wall to parenchyma. For each location on the inner wall contour, the corresponding location on the outer contour was found by a line search in the direction

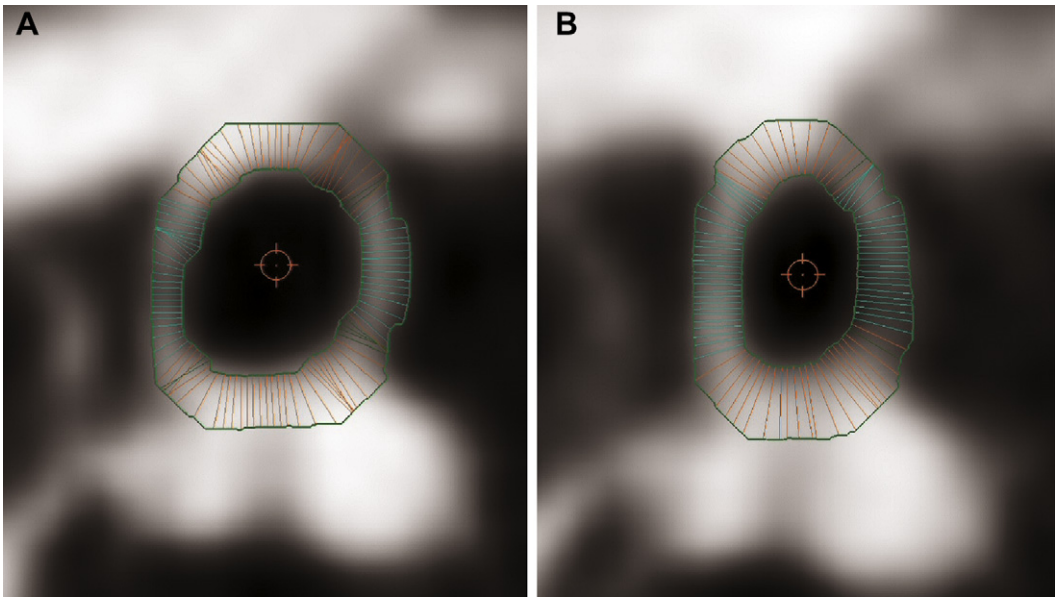

Figure 1 Bronchial measurements. Bronchial measurements in matched cross-sectional CT images through the LB10 at TLC (A) and ~FRC (B). Lumen area is enclosed by the inner wall contour. The green poles indicate the regions used for the calculation of the average wall thickness. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

perpendicular to the inner wall contour. The software automatically excludes subsets of these corresponding pairs that are in the range of the outer contour for which the wall-to-parenchyma transition is not visible (red poles). In addition, the user can exclude/include pairs by selecting a subset of these pairs (red or green poles). Each pair of corresponding points thus yields an estimate of the local wall thickness (Fig. 1, green poles).

Parameters were calculated from the detected contours: lumen area is the area within the inner wall contour and wall thickness is calculated as the average distance between the inner and outer wall contour.

CT-derived global airway distensibility is defined as the difference in bronchial lumen area at the two inspiration levels divided by the corresponding lung volume change due to respiration (from the right or left lung volumes at TLC and ~FRC, measured with Pulmo-CMS).

In order to correlate lumen area change in the 3 bronchi with inspiration level in the related lung lobe we applied new software to determine lobe volumes. This new software was developed in our institute very recently and opt to detect lung fissures in CT scans of the lungs in a semi-automatic way. Due to the low resolution of the CT images in the present study it was in most cases difficult to determine the horizontal fissure in the right lung. Therefore we combined the volumes of the upper and middle right lung lobe as the right "upper" lobe. As a consequence 4 lobes have been defined in this study: left upper lobe, left lower lobe, right upper lobe (as a combination of upper and middle lobe) and the right lower lobe. A very preliminary version of this software package has been used in this study, whereby the user is allowed to set (additional) landmarks on visible fissures to help the software identify the fissures. The software segments the lobes for the left and right lung respectively, and finally shows labeled lung lobes and calculated lobe volumes.

CT-derived lobar distensibility was calculated as the difference in bronchial lumen area divided by the lobe volume change due to respiration (from the right or left lung lobe volumes at TLC and ~FRC).

Validation of the bronchial measurements

Validation of the software for bronchial measurements in CT images was carried out with an in-house developed phantom that contains 30 silicon tubes with varying inner radii and wall thicknesses that are not related to each other. True dimensions of the tubes were obtained using a micrometer with an accuracy of 0.01 mm. The inner radius ranged from 1 to 7 mm with lumen areas between 3.1 and 153.9 mm^2 and wall thickness ranged from 0.3 to 4.7 mm. These tubes were embedded in discs of polyethene foam with a density of approximately 110 g/L, to simulate human lung tissue (Fig. 2). Subsequently, the discs were placed in a Perspex cylinder with a wall thickness of 12 mm, to simulate X-ray absorption by the surrounding thorax (Fig. 2B). The phantom was scanned according to the same image acquisition protocol as for the patient group (slice thickness 5 mm, increment 2.5 mm, FOV 200 mm) and the resulting images were analyzed with the bronchial analysis software with the same settings. The differences between the true and CT-derived lumen area and wall thickness were calculated.

Influence of resolution on bronchial measurements

For evaluation of the influence of slice thickness of the CT scans on bronchial measurements, additional scans and measurements were performed with the bronchial phantom and clinical data acquired with a high-resolution protocol.

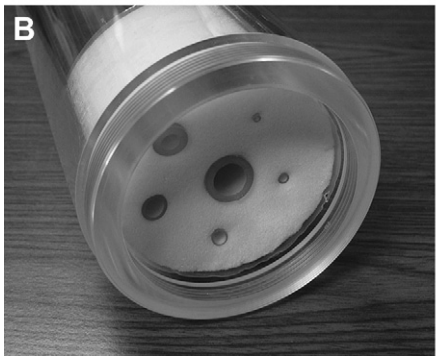

Figure 2 Bronchial phantom. Bronchial phantom showing 30 differently sized tubes embedded in discs of polyethene foam to simulate human lung tissue (A). Subsequently, the discs were placed into a Perspex cylinder with a wall thickness of 12 mm, to simulate X-ray absorption by the surrounding thorax (B).

The bronchial phantom was scanned on the same Toshiba Aquilion 16 detector row scanner (120 kVp; 140 mAs per rotation (350 mA); rotation time 0.4 s; collimation: 16×0.5 mm; pitch factor: 1.4375; and FOV 192 mm). Images were reconstructed with a slice thickness of 0.5 mm and a slice increment of 0.5 mm; an FC02 filter was used to optimize contrast resolution for the bronchial wall.

In addition, we also measured lumen area in CT images of COPD patients that were scanned with high resolution (0.5 mm). For comparison, these images with high resolution were down sampled to a slice thickness of 5 mm with an increment of 2 mm to simulate thick CT slices and bronchial measurements were performed in paired view as described above.

For this additional study we used CT images of 12 randomly selected patients from a group of 30 COPD patients from a former study[19] that were scanned in the supine position with the same CT scanner using the parameters for high resolution scans as stated above with a FOV of 295–400 mm. No contrast media were used. Scans were made during breath hold at full inspiration after three full in- and exhalations, and were obtained in a caudocranial direction to avoid artifacts due to accidental breathing. The Medical Ethics Committee of our institution approved this study, and all patients gave their written informed consent.

Statistics

All statistical analyses were performed using PASW Statistics v. 17.0 for Windows (SPSS Inc. Chicago, Illinois). Paired *t*-tests, Spearman correlations and one-way ANOVA tests were applied to explore differences in bronchial measurements between different inspiration levels and between different bronchi. With linear regression analyses the relation between bronchial lumen (change) and lung volume (change) was estimated. For all statistical analyses a p value less than 0.05 was considered to indicate statistical significance.

Results

Patient characteristics, including lung function, lung CT volume and densitometric data are shown in Table 1.

Validation of bronchial measurements

Twenty-five tubes could be measured by CT and these results are shown in Fig. 3. The lumina of the remaining five tubes were too small for analysis. The differences between true and CT-derived lumen area are plotted against the average of the two values (Fig. 3A). By CT, the lumen areas were systematically underestimated by ca. 4 mm^2 ($p < 0.001$), irrespectively of the size of the lumen. In Fig. 3B a similar plot is shown for wall thickness. Walls thicker than 1.2 mm were overestimated consistently by 0.1 mm, due to blurring effects caused by the limited resolution of the scanner. The overestimation increased dramatically for walls thinner than 1.2 mm (smaller than the surface of two pixels) and therefore tubes with such sizes were not analyzed in this study.

Influence of resolution on bronchial measurements

Measurements of the bronchial phantom scanned at high resolution (0.5 mm slices) gave identical results as measurements in thick 5 mm slices (mean difference: 0.12 ± 0.61 mm^2). By comparing the measurements in thin CT scans with the true measurements, we found that lumen area was systematically underestimated and wall thickness was systematically overestimated in identical ranges as the measurements in thick slices (Fig. 3).

The results of the patient data showed that lumen area measured in thin slices were partly larger than in thick slices (mean difference RB1: 1.55 ± 2.09 mm^2; RB10: 1.00 ± 1.83 mm^2; LB10: 2.39 ± 2.36 mm^2). However, there was no difference in the lumen area measurements between thick and thin slices in the three different bronchi (ANOVA $p = 0.278$).

Bronchial measurements

RB1 and LB10 showed similar-sized lumen areas, while mean lumen area of RB10 was significantly smaller than those of RB1 and LB10 (both at TLC and ~FRC) (Table 2). Lumen area of RB1 was positively correlated with patient

Table 1 Patient characteristics, lung function parameters, CT lung volumes per lung and lobe, 15th percentile point and locality for total lung.

Characteristic	Absolute values	% Predicted values
	Mean ± SD	Mean ± SD
Gender (male/female)	29/15	
Smoker ex/non	11/33	
Age (yr)	51.4 ± 7.7	
Length (cm)	178 ± 8	
Weight (kg)	78.9 ± 12.4	
FEV1 (L)/(%)	1.62 ± 0.67	46.4 ± 18.3
VC (L)/(%)	4.95 ± 1.21	109.4 ± 18.1
FEV_1/VC (%)	33.1 ± 11.6	
FVC (L)/(%)	4.46 ± 1.18	102.3 ± 19.2
TLco (mmol/min/kPa)/(%)	5.37 ± 1.77	51.8 ± 15.7
Kco (mmol/min/kPa/L)/(%)	0.79 ± 0.20	52.2 ± 12.4
CT volume right lung at TLC (L)	4.33 ± 0.80	
CT volume right lung at FRC (L)	3.41 ± 0.79	
CT volume left lung at TLC (L)	3.98 ± 0.74	
CT volume left lung at FRC (L)	3.05 ± 0.74	
CT volume right "upper" lobe at TLC (L)	2.40 ± 0.57	
CT volume right "upper" lobe at FRC (L)	1.99 ± 0.53	
CT volume right lower lobe at TLC (L)	1.85 ± 0.49	
CT volume right lower lobe at FRC (L)	1.36 ± 0.43	
CT volume left upper lobe at TLC (L)	1.99 ± 0.44	
CT volume left upper lobe at FRC (L)	1.61 ± 0.43	
CT volume left lower lobe at TLC (L)	1.90 ± 0.43	
CT volume left lower lobe at FRC (L)	1.37 ± 0.45	
Perc15 (HU)	−953.6 ± 12.9	
Locality (HU)	−33.8 ± 24.1	

length ($R = 0.479$; $p = 0.001$), while lumen area of the two lower lobe bronchi did not correlate.

No significant differences in bronchial measurements were detected between gender (RB1: $p = 0.235$; RB10: $p = 0.307$; LB10: $p = 0.774$) and smoking status (RB1: $p = 0.243$; RB10: 0.875; LB10: $p = 0.580$).

The lumen areas in RB1, RB10 and LB10 were significantly larger at TLC than at ~FRC (Table 2). Bronchial lumen change was significantly correlated with lung volume change (Fig. 4) (RB1: $R = 0.417$, $p = 0.006$; RB10: $R = 0.331$, $p = 0.045$; LB10: $R = 0.455$, $p = 0.005$).

Global airway distensibility (defined as delta airway lumen/delta lung volume of the two inspiration levels) in RB1 was significantly lower than in RB10 ($p = 0.002$) and in LB10 ($p < 0.001$), whilst the distensibility did not differ significantly between RB10 and LB10 (Fig. 5). Gender and smoking status did not influence airway distensibility (gender: RB1: p = 0.270; RB10: $p = 0.337$; LB10: $p = 0.186$; smoking status: RB1: $p = 0.954$; RB10: $p = 0.763$; LB10: $p = 0.729$).

Lobe volume change due to inspiration was 0.407 ± 0.207 L and 0.497 ± 0.259 L for the "upper" and lower right lung lobes and 0.382 ± 0.181 L; 0.525 ± 0.264 L for the upper and lower left lung lobes respectively. As expected inspiration has more influence on lower lobe volumes for both right and left lung (see also Table 1).

Lobar airway distensibility in RB1 was significantly lower than in RB10 ($p = 0.012$) and in LB10 ($p = 0.014$), whilst lobar distensibility did not significantly differ between RB10 and LB10. The distribution pattern of the different lobar distensibilities is similar to that with global distensibility (see Fig. 5). There was no correlation with gender (RB1: $p = 0.378$; RB10: $p = 425$; LB10: $p = 0.276$) or smoking status (RB1: $p = 0.812$; RB10: $p = 0.841$; LB10: $p = 0.890$).

Correlations between bronchial lumen measurements and parameters of lung function are presented in Table 3. Lumen areas at TLC in the lower lobe bronchi were positively correlated with FEV_1%predicted but not at ~FRC (RB10: $R = 0.353$, $p = 0.027$, Fig. 6; LB10: $R = 0.339$, $p = 0.037$). In addition, for RB1 lumen area at TLC there was a positive correlation with VC%predicted ($R = 0.308$, $p = 0.045$) and FVC%predicted ($R = 0.366$, $p = 0.016$).

Bronchial lumen measurements and emphysema severity or emphysema distribution were not significantly correlated (emphysema severity: RB1: $p = 0.202$; RB10: $p = 0.592$; LB10: $p = 0.967$; emphysema distribution: RB1: $p = 0.318$; RB10: $p = 0.106$; LB10: $p = 0.313$).

Discussion

We found that lumen area in the 3rd generation bronchi is dependent on inspiration level in subjects with AATD and that this influence (airway distensibility) is different between upper and lower lobe bronchi. Therefore, changes in lumen area should be studied whilst accounting for lung volume changes over time, in order to estimate progression

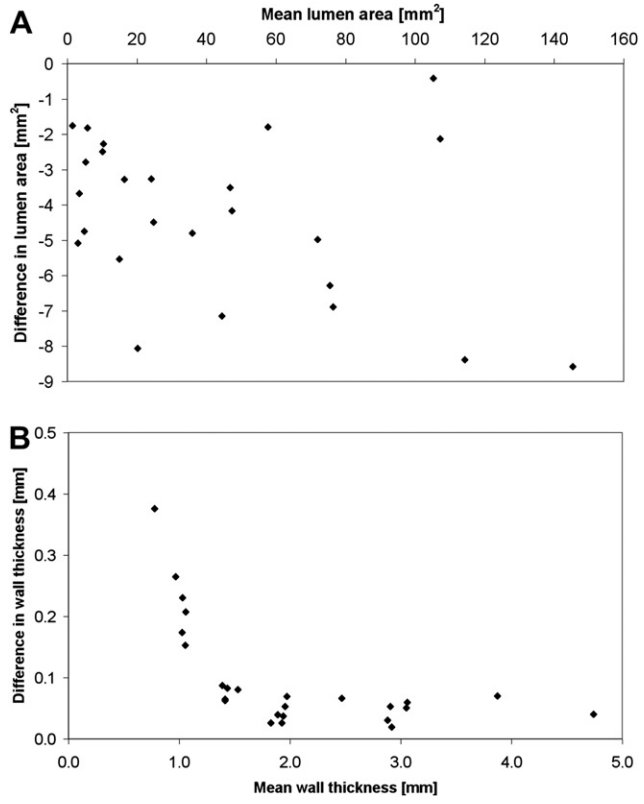

Figure 3 Validation of bronchial measurements. Graphs depicting the results of the validation of bronchial measurements for lumen area (A), and for wall thickness (B). Change is calculated as: measurement with CT − true measurement. Lumen area measured with CT is significantly underestimated with an offset of 3.84 mm^2 independently from lumen area size. For wall thickness the differences are dependent on the size of the measurement.

in bronchial disease while excluding the effects of hyperinflation.

In the present study we excluded measurements of wall thickness due to the low resolution of the CT images. Therefore, this study presents the results of the (distensibility of) lumen area only.

Validation

We used a more elaborate bronchial phantom than in previously published studies.[5,9,20,21] It contained 30 tubes with a wider range of non-related combinations of lumen areas and wall thicknesses (Table 4), showing significant systematic errors in the CT measurement. Lumen area in CT images with both thick and thin slices was significantly underestimated by approximately 4 mm^2 ($p < 0.001$, Fig. 3A) independent of lumen area size, which is different from the observations by Matsuoka.[21] They found an underestimation of 0.3 mm^2 that increased, however, with decreasing lumen area. In addition, underestimations of 27% and 14.9% have been reported.[9,20] Since our underestimation of lumen area was equal for all measurements, no correction was needed for measuring relative changes in this study. We applied a CT scanning protocol optimized for measurement of severity of emphysema rather than for the bronchial tree and this likely accounted for the larger systematic error.

For the phantom data we measured identical lumen area sizes in thick and thin slices. The effect that in patient data lumen areas measured in thin slices were partly larger than in thick slices was expected due to the presence of more partial volume effect in thick slices thus inducing more blurred images and subsequently smaller lumen area. This indicates that the difference in distensibility in the different bronchi we measured in thick slices should be considered a difference in behavior of the bronchi to volume difference. We expect that in thin slices these distensibility differences are more pronounced than in thick slices.

To our knowledge, wall thickness was only validated by Nakano and co-workers[9] and they reported an overestimation by CT for a tube with thin walls, which is in line with our results. We used a range of 25 different thicknesses and found that the errors increased with decreasing wall thickness (Fig. 3B), suggesting that the low number of voxels in each sample reached the detection limit of this method. Therefore wall thickness measurements have been excluded from the present study.

Bronchial lumen versus lung volume

In most previous studies both lumen area and wall thickness were measured in bronchi of different generations and the values were presented as a mean value for all bronchi included.[5,6,8,22] For the lumen area size, however, we found that its dependence on inspiration level is different between bronchi of the same generation and therefore airway measurements should be considered for each bronchus separately. In addition, Fain and co-workers[23] found that normalization of airway measures did not eliminate

Table 2 Comparison of bronchial lumen area between different bronchi (RB1, RB10 and LB10) at different inspiration levels (TLC, ∼FRC) and comparison of change in lumen area from TLC to ∼FRC between the different bronchi.

	RB1		RB10		LB10		RB1 vs. RB10	RB1 vs. LB10	RB10 vs. LB10
	Mean ± SD[c]	*n*	Mean ± SD[c]	*n*	Mean ± SD[c]	*n*	*p* value	*p* value	*p* value
Lumen TLC	22.6 ± 9.6	43	19.2 ± 6.6	39	24.8 ± 8.2	38	0.005	0.480	0.001
Lumen ∼FRC	20.1 ± 8.9	42	14.4 ± 5.8	38	18.6 ± 7.3	37	<0.001	0.389	0.003
Lumen change[a,b]	2.6 ± 2.9**		4.8 ± 4.1**		6.4 ± 4.5**		0.002	<0.001	0.069

[a] Lumen change = lumen at TLC − lumen at ∼FRC.
[b] Significance: **p value $\ll 0.001$.
[c] Mean ± SD: expressed in mm^2 for lumen or in mm for wall thickness.

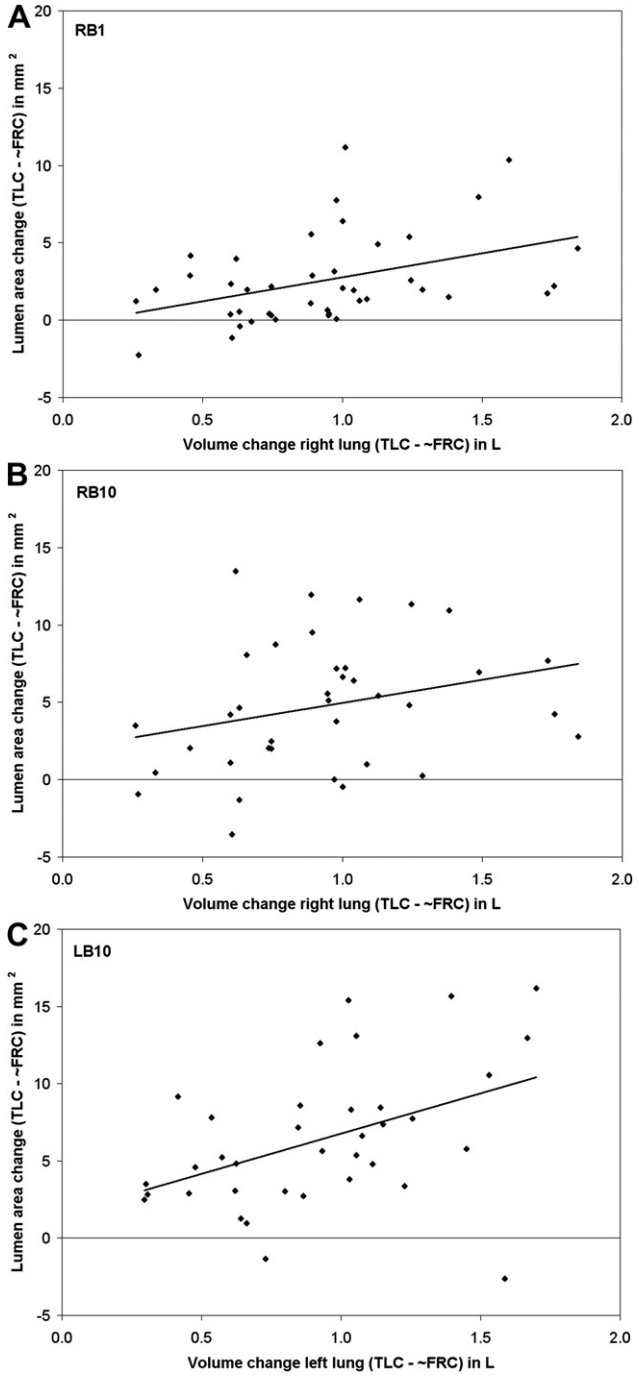

Figure 4 Influence of lung volume on bronchial lumen area. Graphs depicting the relation between change in bronchial lumen area at TLC and ~ FRC and change in volume of the corresponding lung half for (A) the apical segmental bronchus of the right upper lobe (RB1), (B) the posterior basal segmental bronchus of the right lower lobe (RB10) and (C) the posterior basal segmental bronchus of the left lower lobe (LB10).

the dependence on airway generation and thus concluded that studying airway remodeling should be based on airway segment specific analyses rather than averaging across segments. Thereby supporting our statement that bronchial measurements should not be presented as an average value for the whole lung.

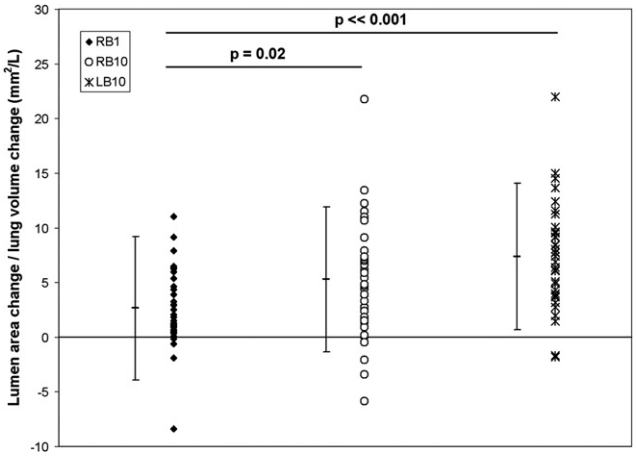

Figure 5 Distensibility. Airway distensibility (bronchial lumen area change/lung volume change of the corresponding lung half) in the three selected bronchi: RB1, RB10 and LB10 (mean $\pm$ standard deviation: $2.6 \pm 3.4\ mm^2/L$, $5.3 \pm 5.3\ mm^2/L$, and $7.4 \pm 4.7\ mm^2/L$, respectively). Lung volume change was similar in the right and left lung volume (0.932 ± 0.387 L and 0.923 ± 0.373 L respectively, see Table 1). Significance of the differences in the distensibility between the different bronchi is indicated by the *p* values.

In the present study we introduced CT-derived airway distensibility as a new bronchial parameter which is independent of lung volume change caused by different inspiration levels. We calculated global and lobar airway distensibility to explore the influence of inspiration of the lung and the lung lobe volumes respectively. The outcome was quite similar: upper lobe distensibility was less than lower lobe distensibility.

The influence of inspiration on bronchial measurements was studied previously by Castagnaro[24] who examined absolute airway lumen size changes induced by airway pressure by nasal insufflation. Insufflation influenced bronchial lumen size in healthy subjects; but had only a mild effect in asthmatics. However, positive pressure may have a different effect than active breathing. In the same year Scichilone[22] published results on inspiration influence in COPD subjects in which ratios of lumen area at total lung volume and at residual volume were used for assessing airway lumen change. They reported that small airways had more lumen area change than larger sized airways and concluded that COPD patients showed less distensibility than healthy subjects. Both studies did not include CT lung volumes to estimate the influence. Unfortunately, the outcomes of Scichilone cannot be compared to our results since they averaged lumen area values over all bronchi. In the present study we assessed airway distensibility per bronchus with lumen areas (Table 2) that fall into the small airway category of Scichilone and showed differences in distensibility between these 3rd generation bronchi (Fig. 5).

Matsuoka and colleagues[21] also calculated lumen ratios during two inspiration levels and found correlations between the 4th and 5th generation bronchi and FEV_1% predicted, but not in the 3rd generation bronchi. By applying the ratio parameter Matsuoka assumes that lung volume differences by respiration are equal for all patients.

Table 3 Spearman correlations of three bronchial lumina (RB1, RB10 and LB10) at TLC with lung function parameters (*R* value; *p* value; ns = not significant).

	RB1 lumen TLC	RB10 lumen TLC	LB10 lumen TLC
FEV_1	0.0341; 0.025	0.438; 0.005	0.385; 0.017
FEV_1%predicted	ns	0.353; 0.027	0.339; 0.037
VC	0.519; 0.001	ns	ns
VC%predicted	0.308; 0.045	ns	ns
FVC	0.487; 0.001	0.319; 0.048	ns
FVC%predicted	0.366; 0.016	ns	ns

This assumption is, however, in conflict with our findings. Therefore, airway distensibility as a volume-corrected parameter per patient may be a valuable parameter that should be further explored in future studies on airway wall remodeling.

After our study was finished, Diaz and co-workers[25] reported on distensibility in 3rd and 4th generation bronchi in the right lung in smoking COPD patients. Their definition for distensibility resembled our approach. Diaz et al. calculated the ratio of the absolute change in airway inner diameter to the cube root of absolute change in lung volume from relaxed exhalation to full inflation and calculated that with whole-lung and lobar CT measures of volume. The differences with the present study are seen in the use of inner diameter versus airway lumen area and in the use of the cube root of volume difference versus absolute volume change. They concluded that distensibility of 3rd and 4th generation bronchi in the right lung lobes was smaller in subjects with emphysema than in controls. Both the study of Diaz et al.[25] and our study show the need for volume correction in bronchial change measurements. This can be explained as follows. In addition to different airway sizes between patients, patients show different amounts in volume change between TLC and FRC (dependent on effort and/or disease severity). In case bronchial lumen area change between the inspiration levels was calculated per patient without volume correction, cross-sectional comparison of the airway change should not be performed. However, such comparisons can be found in literature.[20] By calculating lumen area change per (m)L lung (lobe) volume change between two inspiration levels we introduced the parameter distensibility as a normalized measure of bronchial behavior per amount of volume change. In this way bronchial measurements can be compared cross-sectionally.

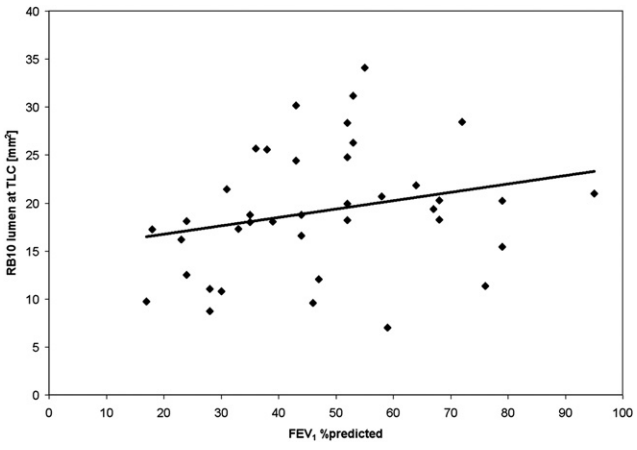

Figure 6 Correlation between bronchial dimensions and lung function. Correlation of bronchial lumen area of RB10 at TLC with FEV_1 %predicted ($R = 0.353$, $p = 0.027$).

The present study provides some insight in the change of lobe volumes between TLC and FRC. The idea was that inspiration in upper and lower lobes could be different and thus have different influences on the different lobe volumes and thereby differently influencing the distensibility of the bronchi. From our results with lobe volume changes we did not find differences in the distensibility calculated with total lung changes compared to calculations with lobe volume changes.

Bronchial measurements versus lung function

Recently, Matsuoka and co-workers[21] studied COPD patients with an identical approach as in the present study. They measured bronchial lumen area and found that expiratory CT measures in bronchi of the 4th and 5th generation were more closely correlated with FEV_1%predicted than inspiratory measures. In contrast, in our study this correlation with FEV_1%predicted was found for the 3rd generation bronchi in the lower lobes but only in scans obtained at TLC level. This contradiction may be explained by the patient groups in both studies that have rather different mean FEV_1 values: their COPD patients had relatively high FEV_1%predicted values ($70.4\% \pm 29.5\%$) as compared to our AATD-group ($46.4\% \pm 18.3\%$). The wide range of FEV_1 values in the COPD group is due to the inclusion of patients from all GOLD classes (according to the Global Initiative for Chronic Obstructive Lung Disease) whereas the AATD subjects constitute a more limited group. Very recently, this stronger correlation of bronchial measurements of more distal bronchi with FEV_1%predicted was also found in AATD patients.[7]

We hypothesized that severity of emphysema could influence the distensibility of bronchi, because lung tissue is lost during emphysema progression. Therefore, the presence of more emphysema may induce less distensibility of the bronchus located in that region, because of loss of elastic recoil. Scichilone and co-workers[22] suggested that damage of lung parenchyma could have the effect that distension of the airways is prevented. Diaz and collegues[25] did find less airway lumen change in emphysema patients, especially in the upper lobes. Since these were smokers, emphysema was assumed to be more localized in the upper lung lobes. As AATD patients (in the present study) have predominantly lower lobe emphysema the influence of emphysema severity should become clear in measurements of the RB10 and LB10 bronchus in this study. However, we did not find a relation between (global or lobar) distensibility in lumen area and emphysema severity in the surrounding lung area in the lower lung lobe (as assessed as Perc15 value in the related vertical lung partition). This relation should be further explored in the future with larger groups of patients with different phenotypes of COPD (e.g. AATD versus general COPD-smokers).

Table 4 Summary of phantom studies in which lumen area and wall thickness or wall area were measured.

	# Tubes	Lumen area (mm^2)	Wall thickness (mm)	Wall area (mm^2)
Nakano et al. (2000)[9]	8	8.0—335.0	0.55—2.25	
Berger et al. (2005)[5]	5	5.6—52.04		6.53—30.16
Hasegawa et al. (2006)[20]	3	1.8—7.1	1	
Matsuoka et al. (2008)[21]	5	1.8—46.0	0.69—1.15	
Present study	25	3.1—153.9	0.3—4.7	

Limitations

We retrospectively analyzed airways from CT images that were optimized for density measurements which produced CT images with a relatively low resolution (slice thickness 5 mm). However, our approach shows that the influence of inspiration level can be detected with measurements of bronchial lumen area even in images acquired with a sub-optimal protocol.

Further, we derived bronchial lumen measurements directly from matched CT slices instead of using perpendicular images reconstructed with interpolation from a bronchial tree derived with software. The low resolution of the CT images did not allow for such an approach.

Lung lobe volumes were assessed by newly developed software that needs further improvement. Therefore more bias may be present in the estimations of lung lobe volumes.

Unfortunately, we were not able to include a control group since no CT data were available of healthy subjects that have been scanned with two inspiration levels. Since the present results were obtained from data from AATD patients only, additional studies are needed to explore whether distensibility differences between bronchi are a general phenomenon in all COPD patients or not.

In conclusion, we found that bronchial lumen area of 3rd generation bronchi is dependent on inspiration level and that this distensibility (defined as bronchial lumen change/lung (lobe) volume change) is different between bronchi in the upper and lower lobes even in CT images acquired with a low resolution protocol. Therefore, changes in lumen area should be studied whilst accounting for the lung volume changes over time in order to estimate bronchial disease while excluding the effects of hyperinflation.

Conflict of interest statement

The authors declare that they have no competing interests.

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