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Research Article

Quantitative High-Resolution CT Analysis of Air Trapping and Airway Thickening in Patients with COPD

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) refers to a heterogeneous group of diseases that are associated with chronic and highly irreversible airway obstruction. COPD may lead to excessive retention of air in the lungs (air trapping) after expiration caused by bronchial airway obstructions (airway wall thickness).

Purpose

To investigate the relationship between air trapping and airway wall thickness as a predictor of abnormal spirometry and consequent significant COPD.

Materials and Methods

Measurements of air trapping and airway wall thickness were performed using expiratory and inspiratory high-resolution computed tomography scans respectively from 21 patients with COPD. Multivariate analysis was employed to investigate the significance of air trapping and wall area in the prediction of lung function using spirometry.

Results

A direct correlation between the percentage of wall area and air trapping ($r=0.497$, $p<0.05$) was demonstrated. In the univariate analysis, wall area and air trapping were predictors of the ratio between forced expiratory volume in one second and the forced vital capacity (FEV1/FVC) (air trapping $r=-0.843$, $p<0.01$; wall area $r=-0.466$, $p<0.05$). However, the multivariate regression analysis indicated that the wall area was not significant when the wall area and air trapping were concurrently applied as a predictor of FEV1/FVC.

Conclusions

This study indicated that wall area did not have a significant role in the prediction of spirometry measurements when the wall area and air trapping were combined. In addition, air trapping may be employed as the sole predictor of abnormal spirometry.

Keywords:

Air Trapping; Airway Wall Thickness; Chronic Obstructive Pulmonary Disease; Respiratory Function Test; High-Resolution Computed Tomography

Introduction

Chronic obstructive pulmonary disease (COPD) is the leading global cause of death, with a prevalence that is predicted to increase [1]. COPD is diagnosed by spirometry, with a post-bronchodilator value of the ratio between forced expiratory volume in the first second and forced vital capacity (FEV1/FVC) < 0.7 [2]. The disease has a heterogeneous presentation as chronic and largely irreversible airways obstruction which usually comprises chronic bronchitis and emphysema. COPD may lead to excessive retention of air in the lungs which is known as air trapping. Air trapping refers to an abnormal retention of air in the lungs, especially during or after expiration, caused by airway obstruction. Computed tomography (CT) scans have been employed to assess pathological changes in the lung parenchyma, such as tissue destruction and chronic inflammation. Currently, high-resolution computed tomography (HRCT) is preferred due to its ability to detect emphysema lesions < 5 mm [3].

Multiple studies have shown a relationship between spirometry values and emphysema, airway wall thickness, and air trapping [4-6]. Grydeland et al. [5] employed measurements of emphysema and airway wall thickness to explain the relationships between respiratory symptoms beyond the information provided by spirometry. They demonstrated that the percentage of low attenuation area (LAA) and airway wall thickness in COPD patients were independently and significantly related to dyspnoea. Mets et al. [7] investigated whether COPD could be diagnosed using only quantitative measures from CT scans. Scans from lung cancer screenings were employed when spirometry was not performed. Their results demonstrated that emphysema, air trapping, and airway wall thickness contained independent COPD diagnostic information. This result suggested that the combination of at least two of the quantitative CT measures may be sufficient for identifying COPD in the absence of spirometry.

No studies have investigated a direct relationship between quantitative air trapping and airway wall thickness in COPD

patients and how this combination is related to pulmonary function test. The present study investigated whether the combination of air trapping and airway wall thickness yielded a better predictive value of abnormal spirometry in patients with COPD.

Materials and Methods

Clinical Data and Lung Function Tests

This study was a retrospective study that was based on data collected from patients who attended the outpatient clinic at Aalborg University Hospital with various respiratory symptoms. All patients had HRCT scans and lung function tests performed as part of their routine clinical examinations of respiratory problems from January 2013 to November 2013.

Twenty-one patients (16 males and five females) were included in the study. All patients were diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, i.e., they had a post-bronchodilator FEV1/FVC < 0.7. The degree of COPD within patients varied from 1 to 4 according to the GOLD guidelines [2], where 1 represents mild and 4 represents very severe. All patients included in the study had two lung function tests performed less than one year prior to the HRCT scans. Lung function tests were performed with patients in a steady state, i.e., no exacerbation within six weeks prior to the test. Data on lung function tests, spirometry, and body plethysmography were collected from hospital records. Demographic data, such as body mass index (BMI), age, and smoking history, were also collected from hospital records. Eighteen of the 21 patients were former smokers, and three of the patients were current smokers.

HRCT Scans

HRCT scans were performed on a Siemens SOMATOM Definition Flash CT scanner with the patient in the supine position. The scan parameters for the inspiratory scan were as follows: 0.6 mm slice thickness, 95 mAs, 120 kVp, and pitch 1.2; the scan parameters for the expiratory scan were as follows: 1.0 mm slice thickness, 100 mAs, and 140 kVp.



Figure 1. Transverse slice of the inspiration phase from a HRCT scan.

The image voxel resolution for the inspiratory scan was $0.58 \times 0.58 \times 0.6$ mm, whereas the image voxel resolution for the expiratory scan was $0.58 \times 0.58 \times 1$ mm.

No contrast agents were employed. The HRCT scans were obtained at full inspiration and full expiration after training the patients on the manoeuvre. The scanner rotation time was 0.5 s, with a total scan time of 1.6 s. (Figure 1) and (Figure 2) show examples of an inspiratory and expiratory scan, respectively.



Figure 2. Transverse slice of the expiration phase from a HRCT scan.

Airway Analysis

In this study, two bronchi were selected for the analysis of airway wall thickness: the apical bronchus of the right upper lobe and one bronchus from the sixth generation in the superior lower lobe of the left lung. The apical bronchus was selected as it is usually observed as a cross-section and is easily identified on CT scans. The sixth generation of the bronchus was selected to enable data collection from a smaller branch, which can be identified in a scan. The bronchi used in the analysis were selected by a medical doctor who was specialised in respiratory medicine.

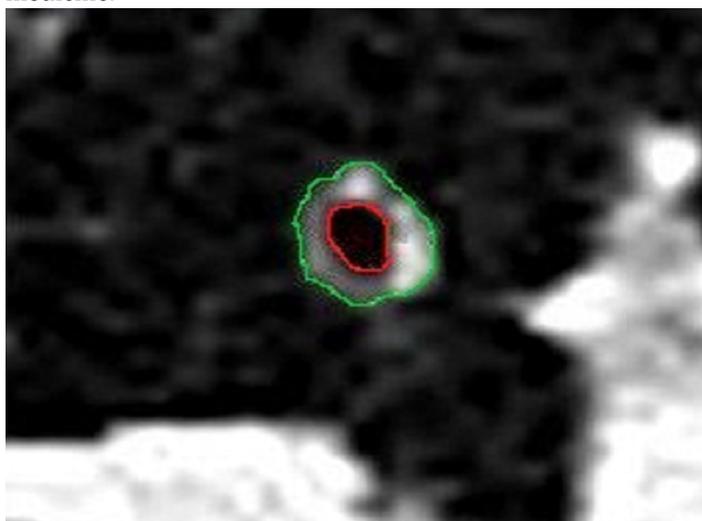


Figure 3. Airway measurement in the apical bronchus. In red delineation of the inner area (Ai) and in green delineation of the outer area (Ao).

tion of the inner area (Ai) and in green delineation of the outer area (Ao).

The semi-automatic airway analysis that was performed on axial images of the inspiratory scans employed the free open-source software "Airway Inspector" [8]. Airway wall thickness was computed using the following parameters: inner airway area (Ai), outer airway area (Ao), wall area (WA), and WA%. These parameters were calculated with the full-width at half-maximum (FWHM) method. (Figure 3) shows the measurements of Ai and Ao in one of the bronchi. Wall area was calculated as the difference between Ai and Ao.

Air-trapping Analysis

During this study, the air trapping analysis was done in two steps. First, the lung parenchyma in the expiratory scans was semi-automatically segmented using a 2D region growing method. Second, a combination of two thresholds were used in order to estimate the air trapping in the lungs. The majority of studies have evaluated the presence of air trapping using the percentage of LAA below a threshold. In this study the upper threshold of -856HU was selected because it is the attenuation of a normally inflated inspiratory lung. Therefore, this concept was based on the fact that the expiratory lung should exhibit higher attenuation than the aforementioned value. A lower threshold of -950 HU was incorporated in order to avoid low density values due to emphysema [9].



Figure 4. Air trapping measurement in red superimposed to the slide from the HRCT scan.

The air-trapping analysis was performed using in-house software in MATLAB R2013b. First, the segmentation was based on a neighbour pixel recursive algorithm, which employed an adaptive threshold to grow the segmented pixel [10]. Once the lungs were segmented, the thresholds of -856 and -950 HU were applied and the percentage of LAA among the thresholds

was computed to estimate the air trapping in the lungs. (Figure 4) shows an example of the air trapping superimposed on the original slide.

Statistics

All statistical analyses were performed using IBM SPSS Statistics v.22. The HRCT findings for air trapping and airway wall thickness were correlated with both pulmonary function values and each other according to the Spearman correlation analysis. Multi-regression analysis was performed to evaluate the relationship between the HRCT measurements and the spirometry and body plethysmography results. A p-value less than 0.05 was considered to be significant.

Results

Table 1. summarises the demographic information of the patients and the results of the two lung function tests performed on the patients. Incomplete patient records were the cause of missing data, as shown in Table 1.

Table 1. Demographic and lung function test data from 21 patients. The numbers in the column Total are the valid number of data points over the total number of patients.

Variables	Mean \pm SD	Range	Total
Age	65.95 \pm 9.97	48 – 81	21/21
BMI	25.13 \pm 3.27	20.4 – 33.6	19/21
Smoking	6.67 \pm 16.83	0 – 50	21/21
FEV1	51.55 \pm 23.30	19 – 103	21/21
FVC	79.20 \pm 19.34	43 – 121	21/21
FEV1/FVC	49.41 \pm 13.23	26.7 – 67	21/21
DLCO	50.66 \pm 23.43	20 – 90.4	10/21
DLCO/VA	63.03 \pm 28.01	32 – 126.9	10/21
RV	173.08 \pm 47.01	108 – 276	12/21
TLC	117.70 \pm 19.38	81.8 – 154	11/21

BMI=body mass index; Smoking=smoking average (packs/year); FEV1=forced expiratory volume in one second (%); FVC=forced vital capacity (%); DLCO=carbon monoxide diffusing capacity (%); VA=alveolar volume (%); RV=residual volume (%); TLC=total lung capacity (%).

Table 2. shows the quantitative analysis results of the airway wall thickness and air trapping as measured on the HRCT scans. The values of the airway measurements represent the average between the two measurements in the apical bronchus and the sixth-generation bronchus.

Table 2. Summary of the quantitative measurements performed in the 21 patients.

Variables	Mean \pm SD	Range
WA%	70.85 \pm 5.46	60.23 – 80.54
WA	26.52 \pm 10.25	13.29 – 58.57
Ai	11.51 \pm 5.79	3.87 – 25.86
Ao	38.03 \pm 15.52	17.17 – 84.43
AT	30.59 \pm 10.02	13.96 – 48.64

WA%=wall area (%); WA=wall area (mm²); Ai=luminal area (mm²); Ao=outer area of the bronchus (mm²); AT=air trapping (%)

The correlation results between the quantitative measurements of air trapping and the measurements of airway wall thickness (WA%, WA, Ai, and Ao) are provided in Table 3. A direct relationship between WA% and the measured air trapping was observed. However, no significant correlations of WA, Ai, and Ao with the measurements of air trapping were observed.

Table 3. Correlation coefficients (r value) derived from Spearman analysis of air trapping and airway wall thickness measurements.

	r Values	p Values
WA%	0.381	<0.05
WA	0.032	NS
Ai	-0.152	NS
Ao	-0.035	NS

WA%=percentage of wall area; WA=wall area; Ai=luminal area; Ao=outer area of the bronchus; NS=nonsignificant.

Table 4. shows the correlation coefficients between the two lung function tests and the percentage of wall area and air trapping measurements obtained from HRCT. A significant relationship between the FEV1/FVC ratio and the measurements of air trapping and WA% was observed. Air trapping also exhibited a significant relationship with Age, FEV1, FVC, DLCO, DLCO/VA and the COPD assessment. Correlation analyses between WA, Ai, and Ao and the lung function test results were also performed; however, no significant values were obtained.

Table 4. Correlation coefficients (r values) derived from the Spearman analysis between airway thickness and air trapping measurements and lung function tests and demographic data.

	WA%		AT	
	r	p	r	p
Age	0.005	NS	0.464	<0.05
BMI	-0.045	NS	0.192	NS
Smoking	-0.315	NS	0	NS
FEV1	-0.343	NS	-0.767	<0.01
FVC	-0.017	NS	-0.527	<0.05
FEV1/FVC	-0.466	<0.05	-0.833	<0.01
DLCO	-0.188	NS	-0.888	<0.01
DLCO/VA	-0.224	NS	-0.685	<0.05
RV	0.406	NS	-0.049	NS
TLC	0.328	NS	-0.128	NS
COPD	0.245	NS	0.760	<0.01

WA%=wall area; AT=air trapping; BMI=body mass index; Smoking=-smoking average; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; DLCO=carbon monoxide diffusing capacity; VA=alveolar volume; RV=residual volume; TLC=total lung capacity; COPD=COPD severity according to GOLD guidelines; NS=nonsignificant.

(Figure 5) and (Figure 6) show the partial regression plots of the multivariate regression analysis between AT and WA and the ratio FEV1/FVC. Both graphs indicate a significant negative relationship between AT and FEV1/FVC and a nonsignificant relationship between WA% and FEV1/FVC.

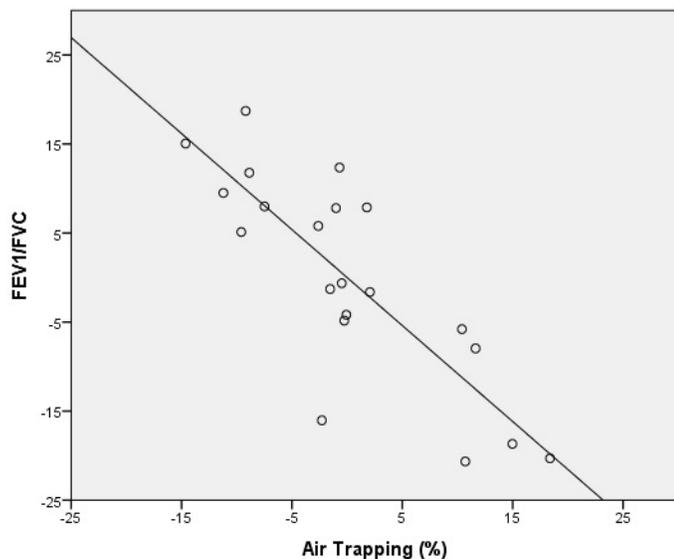


Figure 5. Relationship between air trapping and ratio FEV1/FVC. Results of the model from the multivariate regression analysis for air trapping ($FEV1/FVC=96.013-0.192WA-1.078AT$).

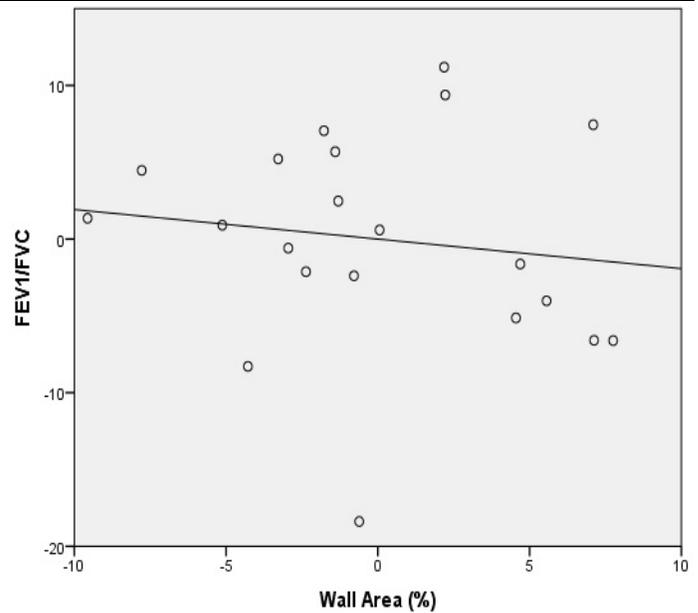


Figure 6. Relationship between the wall area percentage and the ratio FEV1/FVC. Results of the model from the multivariate regression analysis for wall area ($FEV1/FVC=96.013-0.192WA-1.078AT$).

The results of the multivariate analysis of AT and WA versus spirometry and body plethysmography values showed that the addition of WA to AT did not improve the prediction of these lung function tests, as shown in (Fig. 5) and (Fig. 6); therefore, these results were not presented in this paper.

Discussion

This study investigated possible correlations between lung function tests and quantitative measurements of bronchial wall area and air trapping in 21 patients with a COPD diagnosis.

The results of the multivariate regression analysis showed that the airway wall area was not significant when air trapping was used as a predictor of FEV1/FVC, as shown in (Figure 6). Strong associations between air trapping and FEV1, FVC, and FEV1/FVC measurements were demonstrated and the COPD severity has a direct relation with the increase of air trapping; thus, air trapping was associated with a decline in airflow and may be an independent indicator of COPD severity and useful for determining the degree of obstruction in the bronchi. This hypothesis was supported by another study [11], which indicated that air trapping can identify moderate to mild small airway obstructions in subjects who were asymptomatic but exhibited physiological modifications. This study suggested that air trapping was associated with an increase in airway wall thickness. Thus, air trapping can be employed as an indicator of airway wall thickness in small airways when its measurement on HRCT scans is difficult and not feasible. Air trapping was semi-automatically calculated when the user only needed

to predefine the seed point, whereas the analysis of the wall area required an expert to identify and select the bronchi. The air trapping analysis was less time-consuming and prevented inter- and intra-observer variability.

The FWHM method was employed in this study to measure the airway wall thickness and its dimensions due to its objectivity and robustness [12,13]. Although the measurements of airway wall thickness using the FWHM method can be influenced by the reconstruction kernel [14], no consensus has been attained regarding which method is best for measuring airway wall thickness. In addition, no consensus [4,5,15] has been attained regarding which bronchus and how many bronchi are required to obtain a reliable measurement of the airway.

The percentage of LAA established with thresholds of -856 HU and -950 HU in the expiratory scan was employed in this study to estimate air trapping. In this study only the expiratory scan was used to compute air trapping due to it has been demonstrated that expiratory scans show more functional information than inspiratory scans [16]. However, other methods used to calculate air trapping are detailed in the literature, such as the mean lung density ratio between the inspiratory and expiratory scans [4,17]. The upper threshold determination in this study was based on the mean attenuation of a normal lung in the inspiratory phase of -856 HU. Therefore, the attenuation in the expiratory phase should be higher than the aforementioned value [7,18,19]. A threshold of -856 has been successfully used in previous studies [6,20]. Further, it was shown that an optimal threshold to detect air trapping in patients with COPD can vary between -850 and -880 HU due to different scan parameters [9]. A lower threshold of -950 HU was used in order to avoid emphysematous lesions in the air trapping analysis [9,11].

This study had some limitations. First, it was a retrospective study in which data were collected from incomplete patient records. Incomplete patient records were attributed to the notion that body plethysmography is a complicated and time-consuming procedure that does not always gain compliance by all patients. The problem of missing data for some patients may cause a low association between the body plethysmography data and the quantitative measurements. Second, the spirometry and/or body plethysmography were performed within one year prior to the HRCT scans. This time span was extensive; thus, differences in the status of the disease may have existed and the correlation values between the quantitative measurements and the results of these tests may differ slightly. Last, the population was employed as proof of concept due to its small size. However, the size of the population with COPD in northern Denmark [21] is sufficient to perform a longitudinal study to generalise the results. A group of healthy subjects should be included in the new study to compare the results from the multivariate regression analysis performed in the present study with the results of previous studies [6,7].

Expiratory scans may be more sensitive than spirometry in detecting small airway diseases [18]. Spirometry is employed in the assessment of COPD patients and is one of the main tests performed in routine follow-ups; however, it does not provide spatial information on the extent of the disease in the lungs or information on structural abnormalities. Conversely, air trapping enables differentiation of the extension and progression of airflow obstruction. Although this study is only a proof of concept study due to the limitations of the study population, it highlights that the use of air trapping might provide the potentiality of early prognosis prior to the onset of more severe symptoms in patients with COPD. Further, the concept presented in this study will be applied in a future longitudinal study, which will evaluate the precision of air trapping evaluated on HRCT scans as a predictor of the development of COPD progression and the potential effect of treatment.

Conclusion

In conclusion, this study indicated that the bronchial wall area did not have a significant role in the prediction of spirometry measurements when the bronchial wall area and air trapping were combined. Air trapping may also be employed as the sole predictor of abnormal spirometry.

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