Airway dimensions in COPD

Respiratory Medicine (2010) **104**, 1683–1690

available at www.sciencedirect.com

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Airway dimensions in COPD: Relationships with clinical variables

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Received 18 February 2010; accepted 24 April 2010
Available online 11 June 2010

KEYWORDS
COPD;
Airways disease;
Emphysema;
Clinical phenotype

Summary
Background: COPD patients have varying degrees of airways disease and emphysema. CT scanning can differentiate these pathological subtypes. We evaluated airway dimensions and emphysema severity with low dose CT scanning in COPD patients to determine relationships with clinical features of the disease.
Methods: Fifty six patients with COPD had a low dose thoracic CT scan. Airways were analysed using novel software as either proximal (1st and 2nd generation) or distal (3rd to 6th generation); the extent of emphysema was assessed as the percentage of pixels less than −950 Hounsfield units. CT measures were related to clinical features of COPD.
Results: Thicker walls in the proximal airways were associated with clinical features that may represent a bronchitic phenotype (MRC Bronchitis Score; $\beta = 0.20$, $p = 0.003$, Frequent Exacerbations; $\beta = 0.14$, $p = 0.017$, Total St George's Score; $\beta = 0.50$, $p = 0.001$ and body mass index [BMI]; $\beta = 0.26$, $p = 0.049$); these associations were independent of emphysema. BMI was negatively correlated with the degree of emphysema ($\beta = -0.41$, $p = 0.001$). Airway wall thickness was negatively correlated with CT measured emphysema for both proximal and more distal airways ($r = -0.30$, $p = 0.025$ and $r = -0.32$, $p = 0.015$).
Conclusions: CT measured airway dimensions are associated with several clinical measures of COPD; these are related to a bronchitic phenotype and the effect is independent of emphysema.

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doi:10.1016/j.rmed.2010.04.021

Introduction

COPD is a heterogeneous condition in which varying degrees of both airways disease and emphysema are present. Clinically these pathologies tend to be considered as one, quantified by the degree of airflow limitation.[1] There is evidence however, that airway remodelling and emphysema develop from different pathogenic mechanisms.[2–4] As future treatments may target these processes separately,[5] it is important to characterise patients for both the extent of airways disease and emphysema. CT scanning can differentiate these underlying pathological subtypes.[6–10] Studies of emphysema have validated CT lung density measures with both pathology and clinical parameters.[11–14] The relationship between CT measurements of airway dimensions and clinical features of COPD has been less well examined[15–17] and as yet there is no consensus for the best method of assessment.[18]

We hypothesised that airway dimensions and emphysema would relate to distinct clinical parameters of the disease. In this study we investigated the use of novel software designed to assess both airway dimensions and emphysema following low dose thoracic CT scanning in a cohort of COPD patients. We assessed the relationship between these measures and clinical parameters of the disease. In addition, we determined whether airway dimensions were different in patients with or without signs and symptoms suggestive of airway disease, such as symptoms of chronic bronchitis or increased exacerbation frequency.

Methods

Study patients

Current and ex-smokers with a clinical diagnosis of COPD were recruited from primary care and through a respiratory outpatient clinic at the Royal Infirmary of Edinburgh. Chronic airflow limitation was confirmed as a post bronchodilator FEV_1/FVC ratio less than 0.7.[1] Patients were studied when clinically stable; at least six weeks post-exacerbation. Subjects with other respiratory conditions, systematic inflammatory diseases or prescribed regular oral corticosteroids were excluded. Fifty six patients were recruited. All studies were performed with the approval of Lothian Regional Ethics Committee, and written informed consent was obtained from all subjects.

Study design

A structured questionnaire was administered by trained healthcare staff to record baseline characteristics including past medical history and smoking status. Chronic bronchitis was defined using the MRC chronic bronchitis questionnaire, breathlessness with the MRC dyspnoea score, and health related quality of life using the St George's Respiratory Questionnaire (SGRQ). Exacerbation frequency was assessed by patient recall over a one year period: an exacerbation was defined as an increase in symptoms requiring a course of corticosteroids or antibiotics.[19] Patients were classified as frequent (two or more per year) or infrequent exacerbators. Patients performed a 6 min walking test according to ATS guidelines.[20] Spirometry was performed in triplicate (Vitalograph®, Ennis, Ireland) with reversibility to salbutamol (2.5 mg nebulised). Height and weight were measured to calculate body mass index (BMI).

CT acquisition

Study subjects had a low dose thoracic CT scan at full inspiration. Patients were coached to achieve total lung capacity. A 16 slice Toshiba Aquilion CT scanner (Toshiba Medical Systems, Tokyo, Japan) was used with the following parameters: 135 kV, 40 mA, rotation time 0.5 s, 16 $\times$ 1 mm collimation, pitch 1.45, reconstructed at 2.5 mm intervals with 5 mm thick slices (for lung density analysis) and at 1 mm intervals with 1 mm slices (for airway measurement). The Hounsfield Unit (HU) for air was recalibrated using a method similar to that described by Stoel et al[21] to correct for the air offset in Toshiba CT scanners (which is approximately -985 HU instead of the nominal -1000 HU). All CT scans were reviewed by an experienced chest radiologist (JTM); on visual assessment any scans with other lung conditions (eg bronchiectasis, interstitial lung disease) resulted in exclusion of the patient from the study.

CT image reconstruction and analysis

Software was developed to assess airway wall dimensions. A path was plotted by specifying landmarks at selected points along an airway and linked with a smooth 3D spline curve (Fig. 1). To maximise airway data for analysis, airways were measured from the most proximal 1st generation out to the 6th generation distally which is at the limitation of our low dose technique. Airway profiles were then generated on cross-sections orthogonal to this airway path and measurements taken at 1 mm intervals. Rays were projected radially from a seed point at the centre of the lumen (Fig. 2). Using the full width at half maximum (FWHM) technique[22,23] the average airway wall thickness was calculated from portions of the wall surrounding the lumen which had been accepted as valid (ie areas with adjacent blood vessels were automatically excluded, Fig. 2). The lumen wall was detected as the inner half maximum and an ellipse fit to calculate lumen area. Wall thickness was added to the lumen ellipse major and minor axes to calculate the relative areas of lumen and airway wall. The percentage wall area was defined as $\%WA = (\text{outer area of airway} - \text{lumen area})/\text{outer area of airway} \times 100$. %WA was measured for two airways to the 6th generation; one in the right upper lobe via the apical segment bronchus and one in the right lower lobe via the posterior basal segment bronchus. The segmental bronchi of these airways were considered third generation as described by Boyden.[24] A mean of the upper and lower airway dimensions was taken for each of the 2nd to 6th generations; this was done to reduce the effect of distributional differences in disease and to limit the potential for inducing Type 1 errors in the results. Airway generations were designated as proximal (1st and 2nd) or distal (3rd to 6th) and a mean %WA for each group calculated for analysis. This designation was defined by airway luminal

Figure 1 Plotted airway path linked by smooth 3D spline curve.

diameter in order to differentiate large proximal airways (mean diameter 11.0−14.7 mm) from the smaller more distal airways (mean diameter 4.1−1.9 mm) whose dimensions were clearly very different (Table 3). This approach had the added benefit of simplifying subsequent analysis.

The number of pixels below −950 Hounsfield Units was used to quantify low attenuation areas (LAA) as a measure of emphysema. Software was developed to calculate the percentage of pixels below this threshold (%LAA) from the total number within lung parenchyma for each lung CT scan as previously described.[25]

Phantom validation and reproducibility

The validity of our software to make accurate measurements and the reliability and reproducibility of these measurements were independently tested prior to clinical studies. Further details and results of this work are contained within the online supplement.

Statistics

%LAA had a skewed distribution and was thus log transformed. Continuous data were analysed with Pearson's correlation coefficient if normally distributed, otherwise Spearman's rank test was used. Dichotomous data were analysed with an independent samples *t*-test.

Multiple regression modelling was used to test for independent associations in all cases where a significant univariate correlation was found between airway dimensions and clinical measures of disease. For analysis of chronic bronchitis and frequency of exacerbations, binary logistic regression was used. In all other cases, multiple linear regression modelling was used.

In all statistical analyses, significance was taken as $p < 0.05$.

Results

In our cohort of 56 COPD patients there was a range of clinical disease severity, demonstrated in Table 1.

Regarding airway dimensions (Table 2); luminal diameter and airway wall thickness decreased from the 1st to 6th generation distally, while percentage wall area (%WA) increased. Only the 6th generation of airways demonstrated a mean luminal diameter less than 2 mm. The datasets for the 5th and 6th generation of airway are incomplete ($n = 52$ and $n = 35$, respectively); for a small subset of patients these distal airways could not be analysed, they were either destroyed by emphysematous changes or else the lumen was not identified. In Table 2, data are provided as a mean of upper and lower lobe airways; separate analysis of upper and lower airways did not alter the results.

To assess associations between CT measures and clinical features, airway generations have been grouped as proximal (1st and 2nd) or distal (3rd to 6th). A strong negative correlation was found between %WA and emphysema severity (%LAA) in both the larger proximal and smaller distal airways (Table 3).

Several clinical measures of disease were found to correlate significantly with %WA in the proximal airways. Emphysema severity had strong negative associations with both FEV_1 % predicted and BMI. There were no significant

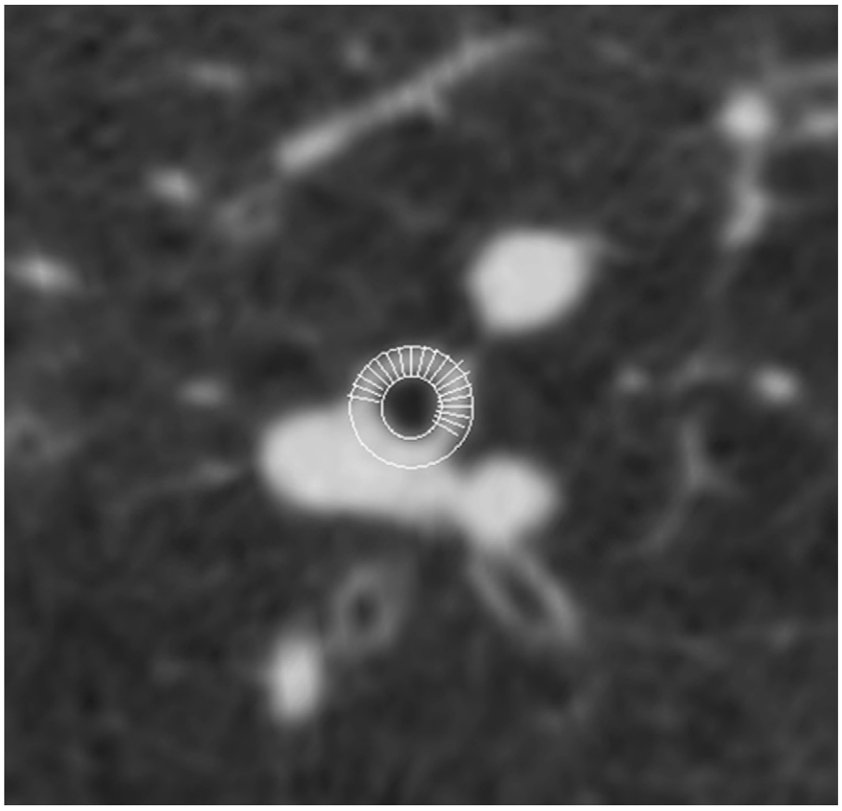

Figure 2 Measuring wall thickness on airway profile using the FWHM technique. Note wall area with adjacent blood vessel has been excluded.

univariate relationships with clinical parameters identified in an analysis using the distal airways.

Further analysis of St George's Respiratory Questionnaire (SGRQ) data demonstrated that the *Symptoms* and *Impact* components were associated with an increase in % WA in the proximal airways ($r = 0.45$, $p = 0.001$ and $r = 0.35$, $p = 0.009$, respectively).

The clinical measures of COPD that had significant univariate associations with %WA in the proximal airways were used as dependent variables in multiple regression models. Proximal airway %WA, emphysema severity (%LAA), age, sex, and height were used as independent variables (Table 4). Despite the negative correlation identified between proximal airway %WA and %LAA (Table 3), there was no evidence of confounding as tested with collinearity diagnostics (data not shown). After adjusting for confounders including age and sex, both thicker airway walls and more severe emphysema were independently associated with total SGRQ score. Interestingly, BMI was negatively associated with emphysema and positively associated with airway wall thickness. In contrast, airway wall thickness was independently associated with frequent exacerbations and symptoms of chronic bronchitis, with only trends to an association with emphysema severity.

Table 1 Demographic data and clinical features. Mean ± standard deviation shown for continuous variables.

n		56
Male sex		41 (73%)
m		67 ± 9
FEV_1 %predicted		52 ± 18
FVC %predicted		81 ± 21
FEV_1/FVC		48 ± 13
Smoking, pack years		47 ± 17
Body mass index,[a] kg/m^2		26 (22−31)
Six minute walking distance, metres		367 ± 122
St George's Respiratory Questionnaire, total score		46 ± 20
Frequent Exacerbators, ≥2/year		30 (54%)
MRC Dyspnoea Score	1	5 (9%)
	2	19 (34%)
	3	16 (29%)
	4	15 (27%)
	5	1 (2%)
Symptoms of chronic bronchitis		27 (51%)

[a] Denotes non-parametric distribution: median (interquartile range). n (%) shown for dichotomous variables.

Discussion

The development of techniques to assess airway wall dimensions and measure emphysema severity in COPD using CT scanning may be important for both researchers and clinicians in charting the progression of disease and response to treatment. In this study, we have shown that patients with symptoms of chronic bronchitis and patients with frequent exacerbations have thicker airway walls than those without, independent of emphysema severity.

Table 2 CT measures of airway dimensions (mean of right upper and lower lobe bronchi) and lung density (%LAA). Mean ± standard deviation given for normally distributed data, median (interquartile range) is provided otherwise (indicated *). Percentage wall area (%WA), wall thickness and luminal diameter are shown for all airway generations. Data for the 5th and 6th generation airways were not obtainable in all cases.

Airway Generation	Diameter (mm)	Wall Thickness (mm)	%Wall Area	n
1	14.7 ± 1.9	3.2 ± 1.0	50 ± 8	56
2	11.0 ± 1.5	2.5 ± 0.7	52 ± 7	56
3	4.1 ± 0.8	2.0 ± 0.4	74 ± 4	56
4	3.0 ± 0.7	1.7 ± 0.3	78 ± 4	56
5	2.2 ± 0.5	1.5 ± 0.3	82 ± 3	52
6	1.9 ± 0.5	1.4 ± 0.2	84 ± 4	35
Lung Density - %Low Attenuation Areas * ($n = 56$)				
6.8 (1.7–19.3)				

Additionally, both severity of emphysema and airway wall thickness are independently associated with poorer health related quality of life, as measured by the St George's Respiratory Questionnaire. Finally, body mass index is positively associated with airway wall thickness, whereas it is negatively associated with emphysema severity. These novel findings suggest that we may be able group individuals into clinically useful CT-defined phenotypes according to their airway wall dimensions and emphysema severity. Crucially, unlike much of the other work in this area, we have adjusted for potential confounders, including age and sex, in our analyses. This is especially important given the well described association between age and reduction in lung density and the known gender differences in emphysema distribution,[25,26] and more recently, airway wall thickness.[27,28]

Using a low-dose CT scan, we have utilised novel software to assess airway dimensions. Both lumen diameter and airway wall thickness reduce from proximal to distal airways. However, the proportion of airway wall thickness to lumen diameter, percentage wall area (%WA), increases from proximal to distal airways. We grouped proximal airways (1st and 2nd generation) with similar luminal diameter/wall thickness and distal airways (3rd to 6th generation) to reduce variability and to simplify analysis. We have shown several associations between the proximal airways and clinical features of COPD. These associations were not found with distal airways. The relationships between airway wall thickness and symptoms of chronic bronchitis, frequent exacerbations and body mass index indicate that measurement of airway walls may allow us to phenotype these patients. A similar large study has also shown that individuals with chronic bronchitis have thicker airways than those without.[29]

Hasegawa et al[30] demonstrated, using CT scans with seven times more radiation than used in this study, that airway wall dimensions are associated with airflow limitation and that the strength of this association increases in more distal airways. We did not show a significant relationship between airway dimensions and FEV_1. When assessing the distal airways, we were only able to measure to the 6th generation in around two thirds of patients, due to obliteration by emphysematous change or inability to establish a suitable lumen. The use of low dose CT scanning in our study may be a reason for the lack of association between airway wall thickness and lung function, and between distal airways and any clinical features. However, a low dose scan protocol can accurately assess larger

Table 3 Univariate associations between clinical and CT measured parameters [airway wall dimensions (%WA) and emphysema severity (%LAA)]. For continuous data, Pearson's correlation coefficient was used unless non-parametric (denoted #) then Spearman's Rho. Dichotomous data were analysed using a *t*-test; mean difference in %WA for each group is provided.

		%Wall area by Airway Generation		% Low attenuation areas(%LAA)
		Proximal 1st and 2nd	Distal 3rd to 6th	
% Low attenuation areas		−0.30*	−0.32*	−
FEV_1% predicted		0.03	0.06	−0.52***
Smoking, pack years		0.07	0.03	−0.06
Body mass index, kg/m^2 #		0.27*	0.16	−0.48*
Six minute walking distance, metres		−0.24	−0.08	0.04
St George's Respiratory Questionnaire	Total	0.37**	0.18	0.20
Exacerbations	0–1	48.8*	76.8	1.41
	≥2	53.0*	77.9	1.87
MRC Dyspnoea Score #		0.26	0.05	0.24
Symptoms of chronic bronchitis	Absent	48.0**	77.1	1.56
	Present	53.5**	77.5	1.86

*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$.

Table 4 Regression analyses of clinical features of COPD and both airway wall thickness and emphysema severity.

Multiple Linear Regression			
Body mass index	Change in BMI	Confidence interval	*p*-value
%Wall area	0.25	0.002 to 0.49	0.049
%Low attenuation areas	−1.788	−2.85 to −0.73	0.001
Age	0.00	−0.18 to 0.18	0.99
Sex	0.18	−2.89 to 0.63	0.46
Height	0.16	−0.04 to 0.36	0.12
$r^2 = 0.36$, $p < 0.001$			
Total St George's Respiratory Questionnaire	Change in SGRQ	Confidence interval	*p*-value
%Wall area	1.47	0.66 to 2.28	0.001
%Low attenuation areas	4.51	1.01 to 8.01	0.013
Age	−0.34	−0.93 to 0.25	0.26
Sex	2.82	−12.28 to 17.91	0.71
Height	−0.001	−0.66 to 0.66	0.99
$r^2 = 0.26$, $p = 0.008$			
Binary Logistic Regression			
Frequent exacerbations	Odds ratio	Confidence interval	*p*-value
%Wall area	1.15	1.03 to 1.29	0.017
%Low attenuation areas	1.61	0.99 to 2.64	0.055
Age	0.93	0.86 to 1.00	0.053
Sex	2.23	0.34 to 14.66	0.41
Height	0.94	0.86 to 1.03	0.19
chi-squared = 15.4, 5df, $p = 0.009$			
Symptoms of chronic bronchitis	Odds ratio	Confidence interval	*p*-value
%Wall area	1.22	1.07 to 1.39	0.003
%Low attenuation areas	1.57	0.96 to 2.56	0.071
Age	0.98	0.91 to 1.05	0.504
Sex	0.52	0.074 to 3.63	0.508
Height	1.04	0.95 to 1.13	0.418
chi-squared = 13.8, 5df, $p = 0.016$			

proximal airway dimensions (which we have found relate to clinical parameters) and make assessment of lung density; the additional advantage of minimising radiation dose is useful for longitudinal studies. Nakano et al[9] demonstrated that measurement of larger more proximal airways can provide a useful surrogate of the airway dimensions distally, since any pathological process causing airflow limitation within the airways is likely to occur at all levels.[31] That study used a combination of CT and lung morphometric measurements in the correlation between large and small airways. Like Nakano, we suspect that the more accurate larger airway measures assessed by CT are representative of distal airway dimensions which, despite being pathologically significant, are beyond the scope of our CT measuring technique.

While this is one of the first studies relating CT measured airway dimensions to clinical features of COPD, other groups have related CT measurements of emphysema severity to clinical features of the disease. We have previously reported a close relationship between emphysema severity and BMI.[25] Makita et al. also showed that individuals with severe emphysema scored visually had a lower BMI and worse health related quality of life than those with mild emphysema, even selecting those with the same degree of airflow limitation.[32] Interestingly, like our cohort, there was no difference in chronic bronchitic symptoms between those two groups. Ogawa et al. also reported a negative correlation between BMI and emphysema.[33] Although the relationship between BMI and airway wall thickness was non-significant in that study, the trend was to a positive association. In addition, similar to our study, Patel and colleagues showed no relationship between emphysema severity on CT and exacerbation frequency.[29] We also found a highly significant negative correlation between airway dimensions and emphysema severity. Such an association has previously been described in two large studies[27,29] and it has been suggested as a mechanism for separating individuals into either an airways or an emphysema phenotype.

Limitations

There currently is no consensus on the best means to identify and label the airway tree. We opted to manually ascertain airway paths; this reduces the need for more sophisticated software but does raise the possibility of observer bias. Our reproducibility data however indicate this was not a major problem. Indeed other investigators have been unable to analyse airway data by generation as a consequence of inaccuracy in fully automated airway mapping.[34] The FWHM technique has been shown here and by other authors to overestimate %WA. However, our validation testing found the associated measurement errors to be within acceptable limits (see online supplement).

Conclusions

In this study we have used novel software to measure airway wall dimensions and emphysema with low dose thoracic CT scanning in individuals with COPD. Airways of less than 2 mm in diameter which are, in part, responsible for airflow limitation in COPD are still beyond the scope of this low dose CT measurement. We have shown that CT measured airway dimensions in the larger, more proximal airways are associated with clinical measures of COPD independent of emphysema severity. Specifically, these clinical features, including symptoms of chronic bronchitis, exacerbation frequency and total St George's score seem to group individuals with thicker airways into a bronchitic phenotype.

Acknowledgements

Financial support provided by the Norman Salvesen Emphysema Research Trust and the National Institutes of Health.

The authors would also like to thank Joyce Barr and Andrew Deans, respiratory research nurses (Royal Infirmary of Edinburgh, UK), for their efforts collecting patient data used in these analyses.

Conflict of interest statement

The authors have no conflict of interest to declare.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2010.04.021

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