COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

informa healthcare

COPD, 11:503–509, 2014
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2014.933952

ORIGINAL RESEARCH

Contribution of CT Quantified Emphysema, Air Trapping and Airway Wall Thickness on Pulmonary Function in Male Smokers With and Without COPD

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Abstract

Emphysema, airway wall thickening and air trapping are associated with chronic obstructive pulmonary disease (COPD). All three can be quantified by computed tomography (CT) of the chest. The goal of the current study is to determine the relative contribution of CT derived parameters on spirometry, lung volume and lung diffusion testing. Emphysema, airway wall thickening and air trapping were quantified automatically on CT in 1,138 male smokers with and without COPD. Emphysema was quantified by the percentage of voxels below –950 Hounsfield Units (HU), airway wall thickness by the square root of wall area for a theoretical airway with 10 mm lumen perimeter (Pi10) and air trapping by the ratio of mean lung density at expiration and inspiration (E/I-ratio). Spirometry, residual volume to total lung capacity (RV/TLC) and diffusion capacity (Kco) were obtained. Standardized regression coefficients (β) were used to analyze the relative contribution of CT changes to pulmonary function measures. The independent contribution of the three CT measures differed per lung function parameter. For the FEV1 airway wall thickness was the most contributing structural lung change (β = –0.46), while for the FEV_1/FVC this was emphysema (β = –0.55). For the residual volume (RV) air trapping was most contributing (β = –0.35). Lung diffusion capacity was most influenced by emphysema (β = –0.42). In a cohort of smokers with and without COPD the effect of different CT changes varies per lung function measure and therefore emphysema, airway wall thickness and air trapping need to be taken in account.

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disorder diagnosed by spirometry when the forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio is below a predefined threshold, ie, airflow limitation is present (1). Airflow limitation is caused by structural lung changes like emphysema and airway wall disease (2). Both can be quantified on chest computed tomography (CT) (3). Emphysema is defined as destruction of the alveoli distal to the terminal bronchioles which lowers tissue densities (4). Airway wall thickening reflects inflammation and remodeling of the bronchi. On expiratory CT scans, localized areas of low tissue density indicate air trapped behind collapsed or obliterated airways and are a surrogate marker for small airway disease.

Keywords: air trapping, airway wall thickness, chronic obstructive pulmonary disease, computed tomography, emphysema, quantitative

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Previous studies showed that emphysema and airway wall thickening on CT negatively relate to the pulmonary function (5, 6). However, data on the small airways, ie, smaller than < 2 mm, are limited (7).

It is not well known to which degree and proportion CT quantified emphysema, airway wall thickening and air trapping relate to different pulmonary function parameters. In this study we therefore investigated the relative contribution of emphysema, airway wall thickening and air trapping to pulmonary function parameters in a cohort of male smokers with and without COPD. Particular attention was paid to the relative contribution of the three CT measures in influencing a wide range of pulmonary function parameters.

Methods

Participants

All participants participated in the Dutch and Belgian Lung Cancer Screening Trial (NELSON trial). To prospectively study COPD, expiratory CT scans were added to the screening protocol in a single centre (8). The study is registered at www.trialregister.nl with trial number ISRCTN63545820. Screening trial participants were current or former (quitted <10 years) smokers between 50 and 75 years with a smoking-history of at least 16 cigarettes/day for 25 years or at least 11 cigarettes/day for 30 years (ie, >16.5 pack-years). Baseline characteristics (age, smoking history and self-reported presence of respiratory symptoms) were collected for all participants. After exclusion of participants with CT segmentation errors ($N = 7$) and missing data on smoking habits ($N = 15$) 1,138 participants were included. The study was approved by the Dutch and Belgian Ministry of Health and by the ethical review board of the University Medical Center Utrecht (UMCU), approval number 03/40. Written informed consent was obtained from each participant.

CT scanning

Low-dose volume scans were acquired after standardized breathing instructions in inspiration and at end-expiration (ie, near the residual volume). All scans were acquired with 16 × 0.75 mm collimation (Brilliance 16P; Philips Medical Systems, Cleveland OH, USA). Settings were adjusted to body weight: 120 kVp (≤ 80 kg) or 140 kVp (> 80 kg) both at 30 mAs for inspiratory scans, and 90kVp (≤ 80 kg) or 120 kVp (>80 kg) both at 20 mAs for expiratory scans. Images with section thickness of 1.0 mm at 0.7 mm increment were reconstructed from lung bases to lung apices using a smooth reconstruction kernel (ie, a soft filter was used, B-filter; Philips).

Computed tomography quantification

All quantifications were performed with CIRRUS Lung 12.03 (http://cirrus.diagnijmegen.nl, Diagnostic Image Analysis Group, Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany).

Quantification of emphysema and air trapping:

The lungs were automatically segmented. A noise reduction filter was applied to decrease the influence of noise on the quantitative measurements. Within the segmented lung volume, the attenuation (in Hounsfield Units, (HU)) of each voxel was assessed to quantify emphysema and air trapping severity (9, 10). CT emphysema was defined as the percentage of voxels in inspiratory CT with an attenuation below –950HU (% < –950). CT air trapping was defined as the expiratory to inspiratory ratio of mean lung density (11).

Quantification of airway wall thickness:

The airway lumen and its centerline were automatically segmented (12, 13). Along the centerline of the airways, inner and outer wall boundaries were determined in cross-sections perpendicular to the local airway dimension at a spacing of 1 mm, based on an intensity-integration approach (12). Cross-sections obtained from the trachea, main bronchi, and bifurcations were automatically excluded, as well as cross-sections for which the airway wall segmentation was automatically determined to have failed.

A linear regression of the square root of wall area versus the lumen perimeter was calculated for the remaining cross-sections and the square root of wall area for a theoretical airway with 10 mm lumen perimeter was calculated, which was used as measurement of airway wall thickness (12, 13). For each CT scan a random selection of cross-sections of the detected airway walls borders was visually inspected to verify measurement accuracy.

Pulmonary function tests

Pulmonary function tests (PFT) were performed with standardized equipment according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (14). No bronchodilation was applied. Spirometry was performed with ZAN equipment (Oberthulba, Germany) and included FEV_1, FVC and FEV_1/FVC. COPD was diagnosed when the FEV_1/FVC ratio was below 70% according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) (1).

The total lung capacity (TLC) and residual volume (RV) were obtained by bodyplethysmography. Lung diffusion measurements were performed with a MasterLab Pro (Erich Jaeger GmbH, Wurzburg, Germany) using the single-breath maneuver method. The test gas contained CO 0.25%, He 9.17% and balance air. A breath-holding period of 10 seconds (Jones and Meade method) and discard/sample volumes of 750 mL were adopted. The rate constant for CO (K_{co}) was expressed as $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$. The ERS reference equations were used to express the measured lung function as percent of predicted.

Statistical analysis

Mean and standard deviation (SD) values were calculated for normally distributed data and median values and inter quartile range (Q1-Q3) for non-normally

distributed data. Distribution of normality was checked visually by Q-Q plots. Because the CT quantified emphysema (% < –950) is a log-normally distributed parameter, we used its ln-transformed value (% < -950_{LN}). Ln-transformation resulted in a normal distribution meeting the requirements of statistical analyses (see the supplementary files for the (Q-Q plots and histograms). The correlation between ln-transformed emphysema, air trapping and airway wall thickness was assessed via the Pearson method.

he relation between the pulmonary function parameter and the three CT scan measures was examined via multiple linear regression. Ln-transformed emphysema, air trapping or airway wall thickness were the primary independent variables. The lung function parameters were the dependent parameters. Pack-years, smoking status (current/ex-smoker), height and age were inserted as correction variables.

In addition to the classical regression coefficients for each independent variable, standardized regression coefficients were also calculated. The latter are unit less expressions of the independent parameter regression coefficients. They are obtained by standardizing these independent parameters and subsequently inserting these into the regression analysis in the same way as the non-standardized parameters. The advantage is that their (absolute) values are well suited to rank the contribution of each independent parameter to pulmonary function: the higher the standardized regression coefficient is, the more relevant is that parameter. The squared multiple correlation coefficients were used to express the percentages of variance explained.

The possible existence of multicollinearity was assessed via the variance inflation factor (VIF) and the normal distribution of the residuals via Q-Q plots. The p-values < 0.05 or less were considered significant. All statistical analyses were carried out via SPSS 20 for Windows (SPSS, Chicago, Illinois, USA).

Results

Demographics

Baseline demographics for the total population and stratified by smoking status (current or former smoker) are shown in Table 1. In total 1,138 subjects were included (608 current and 530 former smokers). Mean (SD) age was 62.5 (5.2) years and the number of pack-years was 41,0 (18,0). The majority (~61%) had no airflow obstruction (FEV_1/FVC >0.70%).

Correlation of emphysema, air trapping and airway wall thickness on CT

The correlation between ln-transformed emphysema, air trapping and airway wall thickness was low. The highest Pearson correlation coefficient found was between air trapping and airway wall thickness, r = 0.320 (p < 0.001). The three CT measures thus behave relatively independently from each other in this cohort. The other correlations coefficients are reported in the supplementary files.

Association of emphysema, air trapping and airway wall thickness with pulmonary function

Table 2 lists the unstandardized regression coefficients (β) of the three CT parameters on the pulmonary function outcomes. These are derived from the multivariate regression analyses with correction for pack-years, smoking status, height and age. To assess the independent

Table 1. Baseline demographics broken down by smoking status

	Total population		Smoking status				
			Current		Former		
	Mean	SD	Mean	SD	Mean	SD	p-value[#]
FEV_1 (% predicted)	94.8	17.6	93.0	17.1	96.9	17.9	<0.001
FVC (% predicted)	104.6	14.5	104.3	14.7	104.9	14.3	0.524
FEV_1/FVC (%)	70.9	9.3	70.0	9.5	72.0	9.1	<0.001
TLC (% predicted)	104.7	14.2	106.3	14.1	103.0	14.3	0.020
RV (% predicted)	111.4	35.2	114.8	36.2	107.7	33.9	0.041
TL_{co} (% predicted)	92.8	17.4	90.2	16.7	95.5	17.6	0.002
K_{co} (% predicted)	87.1	17.4	84.0	17.1	90.3	17.3	<0.001
Wall thickness (Pi10)	2.4	0.51	2.5	0.5	2.4	0.5	<0.001
Percent lung volume <–950 HU[*]	12.4	7.6–18.7	10.6	6.3–16.3	14.9	10.1–18.9	<0.001
E/I-MLD	83.8	6.2	84.2	6.0	83.2	6.4	0.009
Pack-years	41.0	18.0	40.5	17.0	41.6	19.1	0.332
Height (cm)	178.5	6.6	178.6	6.7	178.3	6.5	0.411
Age (years)	62.5	5.2	61.7	4.7	63.5	5.6	<0.001

Mean and standard deviation (SD) are provided. [*]median (Q25 – Q75); [#]unpaired t-test. Pi10 = the square root of wall area for a theoretical bronchus with 10 mm lumen perimeter, $E/I\text{-}_{MLD}$ = the expiratory to inspiratory ratio of mean lung density.

Table 2. Intercept and unstandardized regression coefficients

Parameter	FEV_1	FEV_1/FVC	FVC	TLC	RV	TL_{co}	K_{co}
Intercept	1.437	131.528	0.591	–8.743	–7.117	–6.937	1.546
Age (years)	–0.031#	–0.036#	0.003#	–0.027#	0.013	–0.051#	–0.003#
Height (cm)	0.034#	–0.090#	0.003#	0.081#	0.025#	0.101#	$1.817^{*}10^{-4}$#
Smoking status (former vs. current)	0.034#	0.768#	0.012	–0.103#	–0.054#	0.237#	0.043#
Pack-years	–0.002#	–0.018	0.001#	$1.513^{*}10^{-5}$	0.002	–0.006	–0.001
ln-transformed percent lung volume <–950 HU	–0.153#	–4.512#	0.016#	0.308#	0.188#	–0.499#	–0.098#
$E/I-_{MLD}$	–0.010#	–0.344#	0.003	0.054#	0.052#	0.004	–0.005
Wall thickness (Pi10)	–0.611#	–6.418#	0.036#	–0.301#	0.159#	0.124	0.082

#$p < 0.05$.

contribution of the three CT parameters on lung function impairment the standardized regression coefficients are listed in Table 3 with their p-values (R^2 value). There were no multicollinearity issues: the highest variance inflation factor found in all analyses was below 1.37. The FEV_1/FVC was most affected by emphysema FEV_1 and by airway wall thickness (both $p < 0.001$). The TLC was most affected by air trapping ($p < 0.001$).

From the results in Table 3 the first and second most important lung function influencing CT-scan parameter is listed. This ranking is found in Table 4. The data in this table point at a grouping of effects on lung function outcomes. Airway wall thickness associated most strongly with the FEV_1 and FVC. On the other hand, emphysema associated most strongly with the FEV_1/FVC, diffusion capacity and TLC. Air trapping is of importance for increase of the residual volume.

Discussion

We showed that COPD-associated structural lung changes on CT, i.e. emphysema, airway wall thickening and air trapping, differ in degree of their relative contribution to a wide range of pulmonary function test outcomes. While emphysema associated largest with the FEV_1/FVC, airway wall thickness did with the FEV_1 and air trapping with the residual volume. The results from this study are of importance for radiologists and pulmonologists because it shows that, based on the type and extent of structural CT lung changes, it can be anticipated which pulmonary function parameters will be affected and to what extent they will be affected.

One of the strengths of the current study is that emphysema, airway wall thickening and air trapping were automatically quantified in a large group of (former) smokers with and without COPD and could be related to an extensive set of pulmonary function tests. This is especially important as it is recognized that COPD is a heterogeneous disease not only affecting spirometry but also lung volumes and lung diffusion testing. Some limitations need to be addressed. No subjects with severe COPD (GOLD stage 3) were included. On the other hand, showing that phenotypes based on structural lung changes at CT already affect pulmonary function in smokers without and with mild COPD strengthens the observation. Phenotyping based on CT parameters already seems possible in very early stages of the disease. Furthermore, few studies before focused on subjects with mild disease. Lastly, due to the inclusion criteria only males were included. It has been shown that women have less emphysema than males. Future studies should aim on also including females (15).

Airflow obstruction is caused by a complex mechanism of structural lung changes. Assessing the degree of changes associated with COPD by means of simple spirometry is not sufficient and also lung diffusion testing adds valuable information. Although emphysema causes airflow obstruction by loss of elastic recoil, airway wall disease causes airflow obstruction by airway narrowing. This can also be found in our results. The FEV_1/FVC is a measure most influenced by emphysema. Lung diffusion testing, providing a measure of the capability of the lung to transfer gas, is also most influenced by emphysema.

The FEV_1 is most influenced by airway wall thickness. The fit of the statistical models explaining the spirometry related outcomes (FEV_1, FEV_1/FVC and FVC) was better than the models explaining lung diffusion testing (TLco and Kco). This is probably because lung diffusion testing is also influenced by other factors, like vascular function, which are not taken in account in the current study. However, for determining the relative contributions of either CT quantified emphysema, airway wall thickness or air trapping this will probably not influence the outcomes.

Only a few studies examined the relative contribution of both emphysema and airway wall disease on pulmonary function parameters. A recent study by Camiciottoli et al. (6), showed in 373 COPD subjects with GOLD I to IV that different structural lung changes on CT associate with different pulmonary function tests (6). Lung diffusion testing and total lung capacity (TLC) associated most with CT emphysema. We found a similar pattern in our study. As found by Camiciottoli et al., we report that increasing levels of structural CT lung changes associate with more severe pulmonary function disturbances.

Table 3. Standardized regression coefficients

Parameter	FEV_1		FEV_1/FVC		FVC		TLC		RV		TL_{co}		K_{co}	
	Standardized β	*p*-value	Standardized β	*p*-value	Standardized β	*p*-value	Standardized β	*p*-value	Standardized β	*p*-value	Standardized β	*p*-value	Standardized β	*p*-value
Age	–0.233	<0.001	–0.020	0.340	–0.278	<0.001	–0.112	0.006	0.071	0.118	–0.138	0.003	–0.051	0.267
height	0.327	<0.001	–0.064	0.002	0.452	<0.001	0.448	<0.001	0.180	<0.001	0.363	<0.001	0.005	0.914
Smoking status (former vs. current)	0.074	<0.001	0.123	<0.001	–0.009	0.695	–0.131	0.001	–0.091	0.039	0.194	<0.001	0.249	<0.001
Pack-years	–0.061	0.002	–0.034	0.084	–0.051	0.021	<0.001	0.995	0.036	0.405	–0.057	0.193	–0.038	0.381
ln-transformed percent lung volume <–950 HU	–0.252	<0.001	**–0.548**	<0.001	0.087	<0.001	**0.292**	<0.001	0.235	<0.001	**–0.303**	<0.001	**–0.420**	<0.001
E/I_{-MLD}	–0.094	<0.001	–0.228	<0.001	0.036	0.145	0.276	<0.001	**0.351**	<0.001	0.013	0.799	–0.115	0.020
Wall thickness (Pi10)	**–0.456**	<0.001	–0.353	<0.001	**–0.313**	<0.001	–0.137	0.001	0.096	0.044	0.036	0.449	0.170	<0.001
R^2	0.585		0.580		0.476		0.440		0.297		0.280		0.276	

The bold data represent the highest absolute value of the CT parameter influencing the specific lung function parameter.

Table 4. Ranking of lung function contributing CT parameters based on the standardized regression analyses

	Influencing CT-scan parameter	
Lung function parameter	First ranking	Second ranking
FEV_1	wall thickness (Pi10)	ln-ES950
FVC	wall thickness (Pi10)	–
FEV_1/FVC	ln-ES950	wall thickness (Pi10)
K_{co}	ln-ES950	wall thickness (Pi10)
TLC	ln-ES950	$E/I\text{-}_{MLD}$
TL_{co}	ln-ES950	–
RV	$E/I\text{-}_{MLD}$	ln-ES950

Several studies showed that CT quantified emphysema and airway wall thickness are negatively associated with pulmonary function (16–18). Patel et al. (17) reported in their study of 114 smoking subjects with and without COPD that airway wall thickness correlated best with the RV/TLC. Interestingly, Grydeland et al. (18) demonstrated a weak positive relationship between airway wall thickness and lung diffusion capacity, which we confirm. As a possible explanation they propose the small negative correlation between emphysema and airway wall thickness. When airway wall thickness and lung diffusion capacity decrease, emphysema increases. So, the first two simply may be related because of the change in emphysema.

Air trapping is thought to be associated with disease of the small airways (<2 mm) and may indicate small airway disease better than measurements of airway wall thickness. Few studies assessed the contribution of air trapping to pulmonary function parameters, probably as this requires an additional CT acquisition during expiration (19–21). These studies included small numbers of subjects and again did not compare the relative contribution of air trapping, emphysema and airway wall thickness to several pulmonary function outcomes.

The data of Lee et al. (10) is in agreement with ours and air trapping ($E/I\text{-}_{MLD}$) correlated more to the FEV_1 than to the DLco, $r = -0.890$ and -0.452, respectively. Yamashiro et al. (21) used the ratio of lung volume on inspiratory and expiratory CT, a measure very strongly correlated with $E/I\text{-}_{MLD}$ as used in the current study, but could not find a difference in the degree of correlation within different lung function outcomes, ie, FEV_1, FEV_1/FVC and RV/TLC. Unfortunately, they only performed univariate analyses and did not correct for important factors such as smoking status and pack-years.

It seems there is a large heterogeneity in pulmonary function disturbances in COPD subjects which is probably caused by the difference in extent of underlying structural lung changes. COPD is a complex and heterogeneous disease and it is defined when the FEV_1/FVC is below a predefined threshold, ie, when airflow obstruction is present. However, not only the FEV_1/FVC is decreased in COPD, also other pulmonary function parameters are lower. Results from the current study show that former and current smokers with mainly emphysematous CT changes will have a lower FEV_1/FVC and diffusion capacity. On the other hand, subjects with mainly air trapping, and with only little emphysematous changes will show lower residual volumes but relatively higher FEV_1/FVC values. Only performing spirometry, ie, assessing the FEV_1 and FEV_1/FVC ratio, is not enough to characterize the disease.

Some have proposed to apply a correction of CT quantified emphysema for inspirational level, however there is no consensus of this is preferable (22). By definition correcting for inspirational level by the predicted total lung capacity (TLC) will result in higher emphysema values for those who have a TLC below the predicted reference value and lower emphysema values for those who have a TLC above the predicted reference value. Smoking status (ie, current or former smoker) is known to have a significant effect on CT quantified emphysema. We therefore corrected for this important confounder and also corrected for pack-years and age (23).

Our findings differ from those of the Genetic Epidemiology of COPD (COPDGene) study (24). In that study 4,062 smokers with and without COPD were included. CT measures of air trapping correlated best with the FEV_1 and the FEV_1/FVC, while in our study this was airway wall thickness and emphysema, respectively. In contrast to our study the COPDgene study did not report standardized regression coefficients which is a better suited method to rank the contribution of individual CT measures to pulmonary function. The message of the COPDgene study is the same as ours: to assess impairments in pulmonary function with quantitative CT it is best to use emphysema, airway wall thickness and air trapping measurements.

In conclusion, our study shows that smokers with and without COPD can be phenotyped based on structural lung changes assessed by CT. The degree of emphysema, airway wall thickening and air trapping were largely independent of each other. It is of importance to take emphysema, airway wall thickening and air trapping CT parameters in account when assessing a chest CT.

Declaration of Interests Statement

HK is member of the medical advisory board of Roche Diagnostics. The other authors state that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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