Prediction of the Rate of Decline in FEV1 in Smokers Using Quantitative Computed Tomography

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Abstract
Purpose: To determine if quantitative CT estimates of lung parenchymal overinflation and airway dimensions in smokers with a normal FEV1 can predict the rapid decline in FEV1 that leads to COPD.

Methods: Study participants (n=143; age 45–72yrs; 54% male) were part of a lung cancer screening trial, had a greater than 30 pack years smoking history and a normal FEV1 and FEV1/FVC at baseline (FEV1: 99.4±12.8% (SD), range: 80.2–140.7%; FEV1/FVC: 77.9±4.4 (SD), range: 70.0–88.0%). An inspiratory, multislice CT scan was acquired for each subject at baseline. Custom software was used to measure airway lumen and wall dimensions; the percentage of the lung inflated beyond a predicted maximal lung inflation, the low attenuation lung area with an X-ray attenuation lower than –950HU; and the size distribution of the overinflated lung areas and the low attenuation area was described using a cluster analysis. Multiple regression analysis was used to test the hypothesis that these CT measurements combined with other baseline characteristics might identify those who would develop an excessive annual decline in FEV1.

Results: The annual change in FEV1%predicted was -2.3±4.7 (SD) (range: -23.0 to +8.3%). Multiple regression analysis revealed that the annual change in FEV1%predicted was significantly associated with baseline percent overinflated lung area measured on quantitative CT, FEV1%predicted, FEV1/FVC, and gender.

Conclusion: Quantitative CT scan evidence of overinflation of the lung predicts a rapid annual decline in FEV1 in smokers with normal FEV1.

(Abstract Word Count: 233)
INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease caused by the inhalation of toxic particles and gases that results in destruction of the lung parenchyma, and remodeling of the small airways.(1) Tobacco smoking is the most important risk factor for COPD, but the fact that only a minority of smokers develop COPD strongly suggests that the host response is equally important in the pathogenesis of this condition.(2, 3)

That only a susceptible minority of smokers develop COPD was discovered in a classic study of “the natural history of chronic bronchitis and emphysema” by Fletcher et al.(2) This study showed that over 8 years of follow up only 13% of participants experienced a decline in Forced Expiratory Volume in one second (FEV1), therefore, ended with a final FEV1 that was low enough to satisfy the current diagnostic criteria for COPD.(2) Although recent data suggests that this small fraction may have been an underestimate, the concept that only a minority of heavy smokers develop COPD has not been challenged.(3) By the early 1970s it was recognized that the airflow limitation that defines COPD is caused by a combination of increased resistance in the small conducting airways, and decreased parenchymal elasticity caused by emphysematous destruction.(4, 5) Although many tests have been designed to detect small airway abnormalities at an early and hopefully reversible stage, they have been largely abandoned because they failed to identify the minority of smokers with normal expiratory flows that go on to develop COPD.(6, 7)

The introduction of non-invasive quantitative imaging of both emphysematous lung destruction and airways’ remodeling has provided a fresh approach to detect changes in the anatomy of the peripheral lung. Using these imaging approaches, investigators have shown that persons with normal lung function may have emphysematous destruction in their lungs.(8, 9) These observations led to the hypothesis that early emphysematous destruction might be associated with a subsequent rapid decline in FEV1 that leads to COPD. The present study used computed tomography (CT) scans from subjects participating in a lung-cancer screening study to quantify the inflation of the lung parenchyma, lung area with a lower X-ray attenuation, airway dimensions, and correlated these measurements with serial spirometry that establish a subject’s individual decline in FEV1.

METHODS

Subjects

Subjects in the current study were from the British Columbia (BC) Cancer Agency lung cancer screening program, which is entitled the “BC-Lung Health Cohort”.(10) This sub-cohort is composed of smokers who had normal spirometry at baseline (i.e. FEV1 ≥ 80% of predicted value; the ratio of FEV1 to Forced Vital Capacity, FEV1/FVC, ≥ 70%); at least two spirometry measurements at least 0.5 years apart; and a baseline CT scan obtained using either a GE (GE Medical System, Milwaukee, WI, USA) or Siemens scanner (Siemens Medical Solutions; Erlangen, Germany). The University of British Columbia Clinical Ethics Review board approved the study and all subjects provided informed written consent for the use of all materials and data.

Lung Function
Spirometry was performed using American Thoracic Society guidelines without the administration of bronchodilator.\(^{(11)}\) FEV\(_1\) were expressed as a percentage of the predicted value (i.e. FEV\(_1\)%predicted) calculated using Crapo’s \(^{(12)}\) equations. FEV\(_1\)/FVC was calculated using actual value. The annual change in FEV\(_1\)%predicted (i.e. \(\Delta\)FEV\(_1\)%predicted/yr) was calculated for subjects with 2 visits as: (FEV\(_1\)%predicted at T1 - FEV\(_1\)%predicted at T0) / follow-up yrs. For subjects with more than two visits, \(\Delta\)FEV\(_1\)%predicted/yr was the slope of the regression line, in which all the available FEV\(_1\)%predicted measurements were plotted against age. A negative value of \(\Delta\)FEV\(_1\)%predicted/yr indicates worsening of the lung function.

**CT Technique**

All CT scans were acquired in the volume scan mode at suspended full inspiration with subject in the supine position. No intravenous contrast media was used. These CT scans were acquired using a GE scanner (Lightspeed Ultra, 120kVp, 160mAs, 1.25mm slice thickness, and standard reconstruction kernel) in 36 cases (25\%) and using a Siemens scanner (Sensation 16, 120 kVp, 125mAs, 1.0mm slice thickness, and B35f reconstruction kernel) in 107 cases (75\%). These two image acquisition protocols have been shown to provide comparable CT densitometry measurements.\(^{(13)}\)

**Quantitative CT Analysis**

A quantitative analysis of the lung parenchyma was performed using custom software (EmphyxJ) as previously described.\(^{(13)}\) Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with a prior position-knowledge algorithm. Total lung volume was calculated by summing the segmented pixel area in each slice and multiplying by the slice thickness. For each pixel, the mean CT attenuation (HU) was calculated and converted to density (g/ml) by adding 1000 to the HU number and dividing by 1000,\(^{(14)}\) and the lung inflation (i.e. volume of gas per gram of tissue) was calculated according to Equation 1\(^{(15)}\):

\[
\frac{\text{ml(gas)}}{\text{g(tissue)}} = \text{Specific volume (tissue & gas)-Specific volume (tissue)}
\]

where specific volume is the inverse of density. The density of the lung (tissue and gas) was measured from the CT, and the density of gas free tissue was assumed to be 1.065 g/ml and constant for all subjects.\(^{(16)}\)

The predicted total lung capacity (TLC) was obtained using the equation from Crapo et al: \(^{(17)}\) (Equation 2):

\[
\text{Predicted TLC (ml)} = 59 \times \text{Height (cm)} - 4537 \quad \text{(for women)}
\]
\[
= 79.5 \times \text{Height (cm)} + 3.2 \times \text{Age (yr)} - 7333 \quad \text{(for men)}
\]

The predicted lung weight was obtained by first calculating the predicted body weight using an equation described by Devine \(^{(18)}\) (Equation 3), and then substituting
body weight into the prediction equation for lung weight modified from that originally provided by Shohl (19) (see online supplement) (Equation 4).

\[
\text{Predicted body weight (g) = 45500 + 905.5 x (height (cm) -152.4) (for women)} \quad (3)
\]

\[
= 50000 + 905.5 x (height (cm) -152.4) \quad (for men)
\]

\[
\text{Predicted lung weight (g) = 0.017 x Ideal body weight (g) – 88.12 (g)} \quad (4)
\]

Since TLC is the maximal volume of gas within the lung, dividing it by the predicted lung weight provides an indication of maximal lung inflation. Total overinflated lung volume was calculated by summing the pixel area with a lung inflation value greater than the predicted maximal lung inflation value in each slice, and multiplying by the slice thickness. This overinflation volume was expressed as a percentage of the total lung volume (i.e. %overinflation).

The “upper lung zone” was defined as the region above the carina and zonal predominance was calculated using Equation 5:

\[
\text{zonal predominance} = \frac{\text{upperoverinflation}(\%\text{of totalupperlung})}{\text{loweroverinflation}(\%\text{of totallowerlung})}, \quad (5)
\]

The distribution was considered “upper zone predominant” if the result of Equation 5 was greater than “1”, and considered “diffuse” or “lower zone predominant” if it equaled to “1” or less than “1”, respectively. A “cluster analysis” was used to estimate the size distribution of the overinflated areas.(9) The inverse slope of the log-log relationship of the size of the clusters (number of contiguous voxels that are inflated beyond the predicted value for maximum lung inflation for that individual) versus the number of clusters of that size is the power-law exponent (D). Individuals with diffuse small clusters of overinflated lung will have a steeper slope (i.e. greater D) than individuals with larger-sized overinflated regions. The low attenuation lung area with an X-ray attenuation lower than –950HU, i.e. %LAA(-950), was calculated using the standard threshold approach and used to estimate “emphysema”.(20) The zonal predominance and D were also calculated for %LAA(-950).

Airway wall dimensions were measured for all visible airways cut in cross section on each CT image using the “full-width at half-maximum method” (21). Airway dimensions included: lumen area (Ai), lumen perimeter (Pi), airway wall area (Aaw) and wall area expressed as the percent of the total airway area \((\text{Aaw/ Aaw + Ai}) \times 100\%\). A normalized airway wall estimate: square root of Aaw at Pi-10mm (i.e. \(\sqrt{\text{Aaw at Pi10}}\)).(22) (see online supplement). On average 33.2±3.1 airways were measured per subject.

**Statistical Analysis**

Statistical analyses were performed using JMP software (version 7.0.1 SAS institute, Cary, NC). The primary outcome was \(\Delta\text{FEV1}\%\text{predicted/yr}\), and the explanatory variables were CT measurements of: 1) overinflated lung (i.e. %overinflation, zonal predominance and cluster analysis); 2) emphysema (i.e. %LAA(-950HU), zonal predominance and cluster analysis); and 3) airway dimensions (i.e. Ai, %WA and \(\sqrt{\text{Aaw at Pi10}}\)). Covariates included age, sex, body mass index (BMI), current...
smoking status (i.e. current- or ex-smoker), pack years, and baseline spirometry measurements (i.e. FEV1%predicted and FEV1/FVC). Three multivariate models were used to identify the CT variables that associated with the primary outcome after adjusting for the covariates (overinflation, emphysema, and airway dimensions were tested respectively in model 1, 2 and 3).

To illustrate the relationship between \( \Delta \text{FEV1\%predicted/yr} \) and baseline %overinflation, we divided the 143 subjects into quartiles according to baseline %overinflation (i.e. quartile 1 has the least %overinflation) and compared \( \Delta \text{FEV1\%predicted/yr} \) across four quartiles using the Wilcoxon test. A linear mixed effects model was used to evaluate the annual decline in FEV1(ml/yr) for two groups (i.e. quartile 1&2 and quartile 3&4).(23) Data were expressed as mean±SD and p<0.05 was considered significant.

RESULTS:

Baseline characteristics

Descriptive characteristics of 143 subjects are shown in Table 1, and baseline quantitative CT assessments are summarized in Table 2.

Table 1. Baseline characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>66/77</td>
<td>/</td>
</tr>
<tr>
<td>Age(yrs)</td>
<td>59.5±6.4</td>
<td>44.6─72.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.5±9.8</td>
<td>149.9─195.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.6±14.7</td>
<td>52.2─122.6</td>
</tr>
<tr>
<td>BMI (kg/cm2)</td>
<td>27.7±3.8</td>
<td>18.7─37.5</td>
</tr>
<tr>
<td>Smoking (packyrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers(n=38)</td>
<td>41.5±11.4</td>
<td>30─90</td>
</tr>
<tr>
<td>Ex-smokers(n=105)</td>
<td>49.3±21.0</td>
<td>30─172</td>
</tr>
<tr>
<td>Lung Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1actual (L)</td>
<td>3.2±0.8</td>
<td>1.8─5.7</td>
</tr>
<tr>
<td>FEV1%predicted (%)</td>
<td>99.4±12.8</td>
<td>80.2─140.7</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>77.9±4.4</td>
<td>70.0─88.0</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BMI = body mass index; FEV1 = forced expiratory flow in the 1st second; FEV1%predicted (%) = (FEV1/predicted FEV1) \( \times 100\% \); FVC = forced vital capacity; FEV1/FVC (%) = (FEV1/FVC) \( \times 100\% \).
Table 2. Characteristics of subject’s baseline quantitative CT assessments

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung volume (ml)</td>
<td>5086.2±1350.3</td>
<td>2608.1–9861.1</td>
</tr>
<tr>
<td>Mean lung density (g/ml)</td>
<td>0.2±0.0</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>Lung overinflation %</td>
<td>58.4±16.4</td>
<td>15.9–83.7</td>
</tr>
<tr>
<td>Cluster Analysis</td>
<td>1.5±0.2</td>
<td>1.2–2.1</td>
</tr>
<tr>
<td>upper zone predominant</td>
<td>n= 102</td>
<td>/</td>
</tr>
<tr>
<td>diffuse distribution</td>
<td>n=7</td>
<td>/</td>
</tr>
<tr>
<td>lower zone predominant</td>
<td>n=34</td>
<td>/</td>
</tr>
<tr>
<td>Emphysema %LAA(-950HU)</td>
<td>2.9±2.6</td>
<td>0.2–13.3</td>
</tr>
<tr>
<td>Cluster Analysis</td>
<td>3.1±0.4</td>
<td>2.1–4.4</td>
</tr>
<tr>
<td>upper zone predominant</td>
<td>n= 35</td>
<td>/</td>
</tr>
<tr>
<td>diffuse distribution</td>
<td>n=10</td>
<td>/</td>
</tr>
<tr>
<td>lower zone predominant</td>
<td>n=98</td>
<td>/</td>
</tr>
<tr>
<td>Airway dimensions Lumen area, Ai (mm²)</td>
<td>6.8±2.3</td>
<td>2.1–15.1</td>
</tr>
<tr>
<td>WA %</td>
<td>76.8±3.5</td>
<td>67.5–84.9</td>
</tr>
<tr>
<td>√Awa at Pi10 (mm)</td>
<td>4.4 ±0.2</td>
<td>3.9–5.1</td>
</tr>
</tbody>
</table>

Definition of abbreviations: %overinflation = (volume of overinflated lung/volume of total lung) ×100%; %LAA(-950HU) = (volume of lung areas with a X-ray attenuation lower than -950HU/volume of total lung)×100%; WA % = [airway wall area/(airway wall area + lumen area)]×100%; √Awa at Pi10 (mm) = √Awa for a standardized airway with a internal perimeter (i.e. Pi) of 10mm.

Follow-up measurements of FEV1

Seventy-two of 143 (50.3%) subjects were seen twice over 2.3±0.8 years; 49 of 143 (34.3%) were seen three times over 2.3±1.1 years; and 22 of 143 (15.4%) were seen more than three times over 3.3±1.4 years. The average number of follow-up visits was 2.7±0.8 (range: 2–5 visits) over 2.5±1.1 years (range: 0.5–6.4yrs). ΔFEV1%predicted/yr observed over this time period averaged -2.3±4.7%/yr (range -23.0 to +8.3%/yr).

Risk Factors Associated With Annual Change in FEV1%predicted

Table 3 shows the three multivariate models testing the association between CT measurements and ΔFEV1%predicted/yr. In model 1, %overinflation was inversely associated with ΔFEV1%predicted/yr, whereas neither emphysema nor airway dimensions were associated with ΔFEV1%predicted/yr in models 2 and 3. In addition, in model 1, sex and baseline spirometry measurements were also associated with
ΔFEV1%predicted/yr (male sex: -0.73, 95%CI: -1.43 — -0.03, p=0.04; FEV1%predicted: -0.16, 95%CI: -0.11 — -0.22, p<0.01; FEV1/FVC: 0.19, 95%CI: 0.36 — 0.01, p=0.03).

**Table 3.** Multivariate models testing the association between the quantitative CT measurements and annual change in FEV1%predicted.

<table>
<thead>
<tr>
<th>Model</th>
<th>Measurement</th>
<th>Estimate (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*: Lung overinflation</td>
<td>%overinflation</td>
<td>-0.04(-0.08— -0.02)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Cluster Analysis</td>
<td>-0.49(-11.34—10.35)</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>upper zone predominant</td>
<td>0.02(-0.10—0.14)</td>
<td>0.74</td>
</tr>
<tr>
<td>Model 2*: Emphysema</td>
<td>%LAA(-950HU)</td>
<td>-0.13(-0.47—0.21)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Cluster Analysis</td>
<td>-0.61(-2.68—1.45)</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>upper zone predominant</td>
<td>0.11(-1.38—1.59)</td>
<td>0.89</td>
</tr>
<tr>
<td>Model 3*: Airway dimensions</td>
<td>Lumen area, Ai (mm$^2$)</td>
<td>0.17 (-0.40—0.73)</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>WA %</td>
<td>0.00(-0.53—0.53)</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>√Awa at Pi10 (mm)</td>
<td>1.4(-4.45—7.25)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*: Models were adjusted for sex, age, BMI, smoking status, pack years and FEV1%predicted and FEV1/FVC at baseline.

Definition of abbreviations: %overinflation = (volume of overinflated lung/volume of total lung) ×100%; %LAA(-950HU) = (volume of lung areas with a X-ray attenuation lower than -950HU/volume of total lung)×100%; WA % = [airway wall area/(airway wall area + lumen area)]×100%; √Awa at Pi10 (mm) = √Awa for a standardized airway with a internal perimeter (i.e. Pi) of 10mm.

**Overinflation and Annual Change in FEV1%predicted**

There was a significant linear relationship between CT %overinflation and ΔFEV1%predicted/yr (see Online Supplement). The baseline %overinflation for quartiles 1–4 were 37.1±1.5%, 52.6±0.8%, 67.0±1.1%, and 77.2±0.6% respectively. The corresponding values of ΔFEV1%predicted/yr were -0.9±0.6%, -2.0±0.7%, -2.3±0.7%, and -3.9±1.0% and it were different between quartile 1&2 and quartile 3&4 (p=0.018) (Figure 1).

The average annual decline in FEV1 was 0.047L/yr and 0.068L/yr for quartile 1&2 and quartile 3&4 from the linear mixed effect model (quartile 1&2: FEV1 (L) = 5.220-0.047 × age (yrs); quartile 3&4: FEV1 (L) = 6.25-0.068 × age (yrs)). The FEV1 at each age point of 45, 50, 55, 60, 65, 70, and 75yrs was calculated using these equations for quartile 1&2 and quartile 3&4, and the values were superimposed onto Fletcher’s figure (2) (Figure 2).

**DISCUSSION:**

The present results show that a quantitative CT based estimate of %overinflation using individual predicted maximal lung inflation is an independent predictor of rapid decline in lung function in smokers with normal baseline spirometry. Moreover, the group with a greater %overinflation at baseline exhibited a rate of FEV1 decline beyond
the normal values predicted by Fletcher et al. These results suggest that when the FEV1 is normal, a quantitative structural assessment by CT can distinguish the smokers who will develop COPD from those who will not.

In the current study, we used standard prediction equations for TLC and a prediction equation for lung weight to estimate maximal normal lung inflation for each individual. The average value of predicted maximal normal inflation of the whole group was 5.9±0.2 ml/g (range: 5.3 – 6.5), of which, the corresponding HU was -830±5.3 (range: -846 to -811), and is substantially different from the fixed cutoffs of -950 HU that is commonly used to define emphysema on CT. Importantly, we do not claim that the minimally overinflated tissue identified by this procedure has undergone emphysematous destruction because we have no direct histological evidence. Leopold and Gough’s report based on pathology data concluded that the dilatation and destruction of the respiratory bronchioles that defines centrilobular emphysema, the most common form of emphysema in smokers, is preceded by the disease in the terminal and pre-terminal bronchioles. Therefore, we strongly suspect that the minimal overinflation observed in this study may be caused by either minimal loss in the elastic recoil properties of the gas exchanging tissue and/or an increased resistance in terminal conducting airways due to inflammatory and tissue-remodeling processes, both of which can occur prior to true emphysematous destruction.

The significance of the “overinflation” raised in our study is in agreement with that of the “hyperinflation” described by other investigators. Hyperinflation results from increased lung compliance due to emphysema and expiratory flow limitation, and patients may not perceive the negative results of it until advanced stage because it develops slowly and insidiously over years. Ofir et al examined “hyperinflation” using lung function tests (i.e. total lung capacity, residual volume and functional residual volume) in COPD GOLD stage I and healthy subjects. They found GOLD I subjects had more hyperinflation and it increased as dyspnea intensity increased. Casanova et al found that hyperinflation, independent of the BODE Index, predicted mortality over 34 months follow-up in 689 subjects with COPD. Although the findings that we have obtained with imaging tools are compatible with these studies of hyperinflation, further investigation is required to examine the relationship between these two measures of early disease.

Only a few studies have examined the relationship between quantitative CT measurements of the lung parenchyma and decline in lung function. Remy-Jardin et al examined 111 smokers and non-smokers and reported that subjects with emphysema visualized by radiologists at baseline had a more rapid decline in lung function than did those with normal CT scans. On the other hand, Parr et al and Stolk et al found no relationship between baseline CT emphysema and the subsequent decline in FEV1 in COPD subjects. Those studies recruited many subjects who already have moderate COPD at baseline, which contrasts sharply with the present study that was specifically designed to determine whether CT might identify those smokers that had a normal initial spirometry and subsequently develop COPD.

In contrast to the extent of overinflation, the size and location of the overinflated regions, as assessed by cluster analysis and zonal predominance was less helpful in identifying those “susceptible smokers”. Moreover, although Nakano et al demonstrated that CT measurements of thickening and narrowing of the relatively large
airways serve as surrogate for the pathologic changes in the small airways that are not measurable on CT, we failed to identify a relationship between the CT airway dimensions and ΔFEV1%predicted. There are several possible reasons for this observation. Most importantly, the differences in airway dimensions that accompany a relatively small change of lung function are probably beyond the resolution of CT. Although many investigators have shown relationships between airway wall dimensions and airflow obstruction in cross-sectional studies, the range of lung function in those studies was much larger than in the present study.(21) Secondly, quantitative histological studies have shown that statistically significant airway wall thickening does not become apparent until the later stages of disease (GOLD stage 3 and 4) with an FEV1%predicted <50.(32) Finally, our method for measuring airway dimensions may not be optimal for assessing subtle changes. Hasegawa et al (33) used volumetric scanning to show that airflow limitation in COPD is more closely related to the dimensions of the distal smaller airways (i.e. 5th and 6th generations) than those of proximal larger airways (i.e. 3rd and 4th generations).

Fletcher et al (2) were the first to show a relationship between the initial FEV1 and its subsequent decline and referred to the phenomenon as the “horse racing” effect. However, Burrows et al (34) observed an opposite relationship between ΔFEV1 and initial FEV1, such that the higher the initial FEV1, the more negative the ΔFEV1. They pointed out that this due to “regression toward the mean”, a phenomenon in which subjects performing especially well on their first test show a greater decline because of a poorer performance on subsequent tests. Burrows and Stanescu (6, 34) also observed an association between initial FEV1/FVC and ΔFEV1%predicted, and suggested that FEV1/FVC might provide a more reliable indicator of future loss in FEV1. Our results confirm the findings of Burrows and Stanescu and extend their observations by showing that CT evidence of lung parenchymal overinflation is an independent predictor of decline in FEV1.

Although the lack of an association between smoking intensity (i.e. pack years) and decline in lung function might be a little surprising, this is consistent with other reports in the literature.(35) We also think this lack of association between pack years and the decline in FEV1 supports Fletcher's concept that “non-susceptible smokers” remain unaffected regardless their smoking history. The converse is also true that “susceptible smokers” exhibit a decline in lung function independent of their smoking status.

A limitation of this study is that it was not originally designed as a COPD study but was added on to a lung cancer screening cohort. Thus subjects were not randomly chosen from the population. The follow-up spirometry was arranged at the time of follow-up CT scans which depended on the characteristics of the lung nodule(s) found on the initial CT scan. This means that different numbers of spirometric tests were acquired at different frequencies between subjects. To overcome this limitation, we used ΔFEV1%predicted/yr to normalize the difference in the follow-up period and the number of sampling points among subjects. ΔFEV1%predicted/yr also adjusted for the normal annual loss due to aging, and corrected for differences between females and males.

In summary, we conclude that the quantitative assessment of the lung inflated beyond individually predicted maximal lung inflation on initial CT scans may be able to
identify the “susceptible minority of smokers” who eventually will develop COPD. Our working hypothesis is that the minimally overinflated lung contains the earliest forms of lesions that either increase peripheral airway resistance and/or increase lung compliance by initiating emphysematous destruction.
ACKNOWLEDGEMENTS:
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Competing interests
JC Hogg has served as a consultant, given lectures and participated in advisory boards of several major pharmaceutical companies in the past five years. The total reimbursement for these activities is less than $20000.00.
PD Paré is the principal investigator of a project funded by GSK to develop CT based algorithms to quantify emphysema and airway disease in COPD. With collaborators he has received ~$300,000 to develop and validate these techniques. These funds have been applied solely to the research to support programmers and technicians. PD Paré was also the principal investigator of a Merck Frosst supported research program to investigate gene expression in the lungs of patients who have COPD. He and collaborators have received ~$200,000 for this project. These funds have supported the technical personnel and expendables involved in the project. PD Paré sits on an advisory board for Talecris Biotherapeutics who make anti-one antitrypsin replacement therapy.
DD Sin has received research funding from GlaxoSmithKline and AstraZeneca for projects on chronic obstruction pulmonary disease. DD Sin has also received honoraria for speaking engagements for talks on COPD sponsored by these organizations. HO Coxson received $11,000 in 2005 and $4800 in 2006 and 2007 for serving on an advisory board for GSK. In addition, HO Coxson is the co-investigator on two multi-center studies sponsored by GSK and has received travel expenses to attend meetings related to the project. HO Coxson has three contract service agreements with GSK to quantify the CT scans in subjects with COPD and a service agreement with Spiration Inc to measure changes in lung volume in subjects with severe emphysema. A percentage of HO Coxson’s salary between 2003 and 2006 (15,000 US $/year) derives from contract funds provided to a colleague PD Paré by GSK for the development of validated methods to measure emphysema and airway disease using computed tomography. HO Coxson is the co-investigator (DD Sin PI) on a Canadian Institutes of Health – Industry (Wyeth) partnership grant. There is no financial relationship between any industry and the current study. R Yuan, JC Wong, Y Nakano, S Lam, and AM McWilliams have no competing interests in the content of this manuscript.

Authors’ contributions
Every author has contributed to the design of the study and the drafting and revising of the manuscript. RY, YN and JCW performed the laboratory work and statistical analysis. JCH, PDP, HOC, DDS and SL are the principal investigators of the project, obtained funding for and supervised the project. SL and AMM initially recruited the subjects and DDS provided statistical suggestions. All authors read and approved the final manuscript.

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Figure Legends:

Figure 1. The comparison of ΔFEV1%predicted/yr across the four quartiles of baseline CT %overinflation. The baseline %overinflation was 37.1±1.5%, 52.6±0.8%, 67.0±1.1%, 77.2±0.6% for quartile 1 — 4 respectively. ΔFEV1%predicted/yr was -0.9±0.6%/yr, -2.0±0.7%/yr, -2.3±0.7%/yr, and -3.9±1.0%/yr, respectively, and it was different between quartile 3&4 and quartile 1&2 (p=0.018).

Figure 2. The line with surrounding grey band is the “normal range” (i.e. mean±2SD) of FEV1 (ml) observed in non-smokers by Fletcher et al (2). Open circles and triangles represent an extrapolation of the data from the current study. Open circles are data from quartile 1&2, in which, smokers had less %overinflation at baseline and had a 0.047L annual decline rate in FEV1. Triangles are data from quartile 3&4, in which, smokers had more %overinflation at baseline and had a 0.068L annual decline rate in FEV1.
REFERENCE
Prediction of the Rate of Decline in FEV1 in Smokers Using Quantitative Computed Tomography

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Online Data Supplement
METHODS

**Lung Weight Prediction:**

The X-ray attenuation values of the lung were analyzed using custom software (EmphylxJ) as previously described.\(^{(1-3)}\) CT lung volume was calculated by summing the voxels. Lung weight was calculated by multiplying the lung volume (ml) by the CT density (g/ml) as previously described.\(^{(1-3)}\) Since the CT scanner measures the density of the lung parenchyma which is the mass of the lung tissue per volume of lung. The inverse of density is specific volume which, in this case includes the volume of tissue and gas per gram of tissue. Therefore, to calculate the inflation of the lung, expressed as the volume of gas per gram of tissue (ml gas/g tissue), the specific volume of tissue must be subtracted from the specific volume of the tissue and gas using the following equation: \(^{(2)}\)

\[
\frac{\text{ml(gas)}}{\text{g(tissue)}} = \text{Specific volume (tissue and gas)} - \text{Specific volume (tissue)} \tag{1}
\]

where specific volume is the inverse of density. The density of the lung (tissue and gas) was measured from the CT, and the density of tissue was assumed to be 1.065 g/ml and was assumed constant for all subjects.\(^{(4)}\)

Predicted values for normal total lung capacity (TLC) were obtained using the prediction equation reported by Crapo et al.\(^{(5)}\)
For women;

\[ \text{Predicted TLC (ml)} = 59.0 \times \text{Height (cm)} - 4537 \] \hspace{1cm} (2)

For Men;

\[ \text{Predicted TLC (ml)} = 79.5 \times \text{Height (cm)} + 3.2 \times \text{Age} - 7333 \] \hspace{1cm} (3)

Predicted values for normal lung weight were obtained by first predicting ideal body weight using an equation described by Devine:(6)

For women;

\[ \text{Ideal Body weight (g)} = 45500 + 905.5 \times (\text{height (cm)} - 152.4) \] \hspace{1cm} (4)

For men;

\[ \text{Ideal Body weight (g)} = 50000 + 905.5 \times (\text{height (cm)} - 152.4) \] \hspace{1cm} (5)

And then substituting ideal body weight into Shohl’s prediction equation for lung weight(7)

\[ \text{Lung weight (g)} = 0.015 \times \text{body weight (g)} \] \hspace{1cm} (6)

Equation 6 was re-derived for subjects with a smoking history using CT measured lung weights to obtain the coefficients for Equation 7:

\[ \text{Modified equation: Lung weight (g)} = 0.017 \times \text{Ideal body weight (g)} - 88.12 \ (g) \] \hspace{1cm} (7)
Equation 7 was derived from a previous study in our institution by comparing the relationship between the lung weight measured using CT and the lung weight measured gravimetrically following resection. The purpose of that study was to validate and update Shohl’s lung weight prediction equation. The new lung weight prediction equation was then tested in a second set of subjects undergoing lung resection.

Five lung specimens were received from subjects who underwent pneumonectomy for bronchogenic carcinoma. The lung specimens were inflated to a transpulmonary pressure of 20cm H2O and scanned using a GE HiSpeed scanner (General Electric Medical Systems, Milwaukee, WI) using the following parameters: 120kV, 40mAs, 7.0 mm collimation and reconstructed using an intermediate spatial frequency reconstruction algorithm (i.e. GE: ‘Standard’). The CT lung weight was calculated by multiplying the CT measured total lung volume by the CT estimated lung density as previously described. The fresh specimen was weighted immediately after the surgery. The relationship between the CT lung weight and the gravimetric lung weight was tested using simple linear regression analysis and p value less than 0.5 was considered significant.

Following this step, the CT measured lung weight was compared to the predicted lung weight using Equation 6 in 45 individuals from a lung cancer screening trial. All subjects received a CT scan using a GE HiSpeed scanner and same protocol as described above. The relationship between the CT lung weight and predicted lung weight using Shohl’s equation (i.e. Equation 5) was tested using simple linear regression analysis and the relationship was used to generate a new prediction equation for lung weight (i.e. Equation 7).
Finally the new lung weight prediction equation was used to predict the lung weight in 23 lung pneumonectomy specimens (12 left and 11 right sided), in which, the fresh specimen was weighted immediately after the surgery. The predicted lung weight was calculated using Equation 7 and the assumption that the right lung accounts for 55% and the left lung accounts for 45% of total lung weight (2). The relationship between the gravimetric lung weight and the predicted lung weights using Equation 7 was tested using simple linear regression analysis and p value less than 0.5 was considered significant.

**CT Measurement of Airways:**

Airway wall dimensions were measured for all visible airways cut in cross section on each CT image using the “full-width at half-maximum method” (10). In this approach, a seed point is placed in the lumen of an airway. Sixty-four rays are projected from the seed point through the airway wall and into the lung parenchyma and the apparent X-ray attenuation values along the ray are calculated. This technique assumes that apparent X-ray attenuation increases from a minimum within the lumen to a maximum within the airway wall and then decreases again as the ray passes into the lung parenchyma. The inner boundary of the airway wall is set at the point on each ray where the apparent X-ray attenuation value is half way between lumen minimum and the wall maximum while the outer boundary is set as the point half way between the wall maximum and the parenchymal minimum. These points on the rays are then connected using a spline function. The lumen area (\(A_i, \text{mm}^2\)) and airway wall area (\(A_{wa}, \text{mm}^2\)) are measured by calculating the number of CT voxels contained within the inner boundary.
and between the inner and outer boundary respectively. The lumen perimeter ($P_l$) is the length of the inner boundary. The percent of the total airway area that is occupied by airway wall (wall area percent, WA%) is calculated by dividing $A_{aw}$ by the sum of $A_{aw} + A_i$, and expressed it as a percentage of the sum. To avoid potential bias issues surrounding different distribution of airway sizes between subjects, a standardized measurement of airway wall area ($P_{i10}$) was derived for each subject by plotting the square root of the airway wall area against the internal perimeter of each measured airway within each subject. The resulting regression line from each subject was used to calculate the square root of wall area for a “theoretical airway” with an internal perimeter of 10 mm ($P_{i10}$) (Figure E1). (11, 12)

**Statistical Analysis**

The relationship between the outcome – annual change in FEV1%predicted (i.e. $\Delta FEV1%\text{predicted/yr}$) and baseline CT %overinflation in 143 subjects was tested in simple linear regression analysis and $p$ value less than 0.05 was considered significant.

**RESULTS**

**Lung weight:**

The fresh lung weight from the first five resected specimens was $697\pm333$ g and the lung weight calculated on CT was $655\pm307$ g. There was significant linear relationship between the two measurements (Figure E2) suggesting that CT lung weight can be used as a surrogate of gravimetric lung weight.
In 45 subjects (demographics shown in Table E1), the lung weights measured using CT were 989 ± 183 g while the predicted lung weights using Shohl’s equation (i.e. Equation 6) were 928±134 g. There was a significant linear relationship between the two measurements (r=0.85, p<0.001) with a slope of 1.16 g and an intercept of 88.12g (Figure E3). Therefore, Shohl’s lung weight prediction equation can be modified as follows:

\[
\text{CT lung weight (g)} = (1.16 \times \text{Shole’s predicted lung weight}) - 88.12
\]

\[
= 1.16 \times (0.015 \times (\text{predicted body weight}) - 88.12
\]

\[
= 0.017 \times \text{predicted body weight} - 88.12
\]

Finally, in 23 subjects who underwent pneumonectomy (demographics shown in Table E2), the gravimetrically measured lung weights were compared to the predicted lung weights using the new modified lung weight prediction equation (i.e. Equation 7). The gravimetric weights were 531 ± 213 g while the predicted lung weights were 514 ± 186 g. There was a significant linear relationship between these two measurements (r=0.81, p<0.001) (Figure E4) indicating that the new prediction equation based on Devine’s ideal body weight and the modified Shohl’s lung weight equation give a reliable estimation of gravimetric lung weight.

**Correlation between annual change in FEV1 and baseline CT %overinflation:**

There is a significant linear relationship between annual change in FEV1%predicted (i.e. ΔFEV1%predicted/yr) and baseline CT %overinflation in 143 subjects (Figure E5), indicating that the baseline parenchymal anomaly can be used to predict the subsequent deterioration in airflow limitation.
References:


Table E1. Demographic characteristics of 45 subjects from a lung cancer screening trial

<table>
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<tr>
<th></th>
<th>mean±SD</th>
<th>range</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59.3±7.7</td>
<td>45.3 – 74.6</td>
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<tr>
<td>Male/Female</td>
<td>14/31</td>
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<tr>
<td>Height (cm)</td>
<td>168.9±8.1</td>
<td>153.7 – 188.0</td>
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<tr>
<td>Weight (kg)</td>
<td>74.7±12.1</td>
<td>57.2 – 99.8</td>
</tr>
<tr>
<td>FEV1% Predicted</td>
<td>90.0±19.7</td>
<td>56.0 – 133.0</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>72.9±7.2</td>
<td>52.0 – 84.0</td>
</tr>
<tr>
<td>Smoking Pack Years</td>
<td>45.5±12.3</td>
<td>29.0 – 90.0</td>
</tr>
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Table E2. Demographic characteristics of 23 subjects undergoing pneumonectomy

<table>
<thead>
<tr>
<th></th>
<th>mean±SD</th>
<th>range</th>
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</thead>
<tbody>
<tr>
<td>N=23</td>
<td></td>
<td></td>
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<tr>
<td>Age (yrs)</td>
<td>58.5±3.1</td>
<td>17.0 – 73.0</td>
</tr>
<tr>
<td>Male/Female</td>
<td>10/13</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164±9.8</td>
<td>146.0 – 185.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.3±17.5</td>
<td>40.0 – 124.0</td>
</tr>
<tr>
<td>FEV1% Predicted</td>
<td>87.4±14.4</td>
<td>62.0 – 114.4</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>74.9±9.1</td>
<td>49.0 – 86.6</td>
</tr>
<tr>
<td>Smoking Pack Years</td>
<td>38.7±32.9</td>
<td>0.0 – 122.5</td>
</tr>
</tbody>
</table>
Figure E1. Plotting the square root of the airway wall area against the internal perimeter of each measured airway in one subject. The regression line was used to calculate the square root of wall area for a “theoretical airway” with an internal perimeter of 10 mm (i.e. Pi10) for each subject.

Figure E2. There was a significant correlation between the CT lung weight and gravimetric lung weight in five resected specimens (r=0.99, p<0.001). The regression line is very close to the identity line (dashed line).

Figure E3. The relationships between lung weights measured on CT and those predicted by using Devine’s body weight prediction equation (i.e. Equation 5) and Shohl’s lung weight equation (i.e. Equation 6) in 45 individuals in a lung cancer screening trial (r=0.85, p<0.001).

Figure E4. The relationships between gravimetric lung weights and lung weights predicted using new lung weight prediction equation (i.e. Equation 7) in 23 subjects who underwent pneumonectomy (r=0.81, p<0.001).

Figure E5: The association between the %overinflation on baseline CT and the annual rate of decline in FEV1%predicted (i.e. ΔFEV1%predicted/yr) (r= -0.3, p=0.001).
The graph shows the relationship between the square root of wall area (mm) and the internal perimeter (Pi, mm). The regression equation is given as:

\[ y = 0.2168x + 2.5995 \]

with a correlation coefficient \( R = 0.91 \) and a significance level of \( p < 0.001 \).

The SQRT at Pi=10mm is indicated on the graph.
The equation of the line is:

\[ y = 1.0757x - 7.8304 \]

with a correlation coefficient:

\[ r = 0.99, \ p < 0.001 \]
y = 1.1611x - 88.118

r = 0.85, p < 0.001

CT lung weight (g)
predicted lung weight from Shole's and Devine's equations (g)
Gravimetrically measured lung weight (g)

\[ y = 0.9306x + 53.047 \]

\[ r = 0.81, p<0.001 \]
The scatter plot shows the annual change in FEV1%predicted (Δyr) against %overinflation on baseline CT. The correlation coefficient is $r = -0.3$, with a significance level of $p = 0.001$. The data points are distributed along a trend line, indicating a negative correlation between the two variables.
Prediction of the Rate of Decline in FEV1 in Smokers Using Quantitative Computed Tomography

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