Airway Count and Emphysema Assessed by Chest CT Imaging Predicts Clinical Outcome in Smokers

Alejandro A. Diaz, MD; Clarissa Valim, MD, PhD; Tsuneo Yamashiro, MD; Raúl San José Estépar, PhD; James C. Ross, MS; Shin Matsuoka, MD, PhD; Brian Bartholmai, MD; Hiroto Hatabu, MD, PhD; Edwin K. Silverman, MD, PhD; and George R. Washko, MD

Background: Recently, it has been shown that emphysematous destruction of the lung is associated with a decrease in the total number of terminal bronchioles. It is unknown whether a similar decrease is visible in the more proximal airways. We aimed to assess the relationships between proximal airway count, CT imaging measures of emphysema, and clinical prognostic factors in smokers, and to determine whether airway count predicts the BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index.

Methods: In 50 smokers, emphysema was measured on CT scans and airway branches from the third to eighth generations of the right upper lobe apical bronchus were counted manually. The sum of airway branches from the sixth to eighth generations represented the total airway count (TAC). For each subject, the BODE index was determined. We used logistic regression to assess the ability of TAC to predict a high BODE index (≥7 points).

Results: TAC was inversely associated with emphysema (r = -0.54, P < .0001). TAC correlated with the modified Medical Research Council dyspnea score (r = -0.42, P = .004), FEV₁ % predicted (r = 0.52, P = .0003), 6-min walk distance (r = 0.36, P = .012), and BODE index (r = -0.55, P < .0001). The C-statistics, which correspond to the area under the receiver operating characteristic curve, for the ability of TAC alone and TAC, emphysema, and age to predict a high BODE index were 0.84 and 0.92, respectively.

Conclusions: TAC is lower in subjects with greater emphysematous destruction and is a predictor of a high BODE index. These results suggest that CT imaging-based TAC may be a unique COPD-related phenotype in smokers.

COPD is defined as incompletely reversible expiratory airflow obstruction due to emphysematous destruction of the lung parenchyma and remodeling of the small airways. Although these two processes are classically thought of as being pathologically distinct, with emphysema being a purely parenchymal disease, an early report found that emphysematous lungs tended to have fewer visible small airways than those with less parenchymal destruction. More recently, McDonough et al and Hogg et al substantiated this finding using micro-CT scanning. They found that subjects with severe disease had a significant decrease in their number of terminal bronchioles, presumably lost during the destructive parenchymal process that manifests microscopically and macroscopically as emphysema.

Although Montaudon et al reported no differences in airway count in smokers and nonsmokers with normal lung function, we and other groups have observed anecdotally that subjects with severe emphysema on their chest CT scan tend to have fewer proximal airways available for quantitative analysis. One possible explanation for this finding is that the loss of airways associated with emphysema is not limited to the terminal bronchioles and beyond but extends more proximally as well. Our goal was to assess objectively...
the relationship between central airway count and CT scan burden of emphysema in smokers. Using volumetric CT scans obtained as part of the Lung Tissue Research Consortium (LTRC) (www.ltrcpublic.com), we undertook a detailed examination of the airways originating from the apical bronchus of the right upper lobe (RB1). Our hypothesis was that subjects with the greatest burden of emphysema would have the fewest visible airways in the proximal tracheobronchial tree. We also sought to determine whether airway dropout was predictive of the BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index, which is a multidimensional score for predicting mortality in subjects with COPD.

Materials and Methods

The study and manuscript were approved according to the procedures of the LTRC detailed elsewhere. This study was also approved by the Institutional Review Board at Brigham and Women’s Hospital.

Subject Selection

This is a convenience sample from the LTRC. Subjects were eligible if they had a ≥10 pack-year smoking history and a high-resolution volumetric CT scan. Among 125 subjects meeting these initial criteria, 16 were then eliminated because they had a bullous disease of the right lung or an artifact introduced by an intra-venous catheter or pacemaker that precluded visual examination of the airways (4); a large mass in the right upper lobe (4); or evidence of previous surgery on the right lung (8). A total of 109 subjects were subsequently deemed eligible for this study. Following densitometric assessment of CT scans (see “Imaging Assessment”), 50 subjects were selected and clustered into two groups: 25 with a high (≥25%) and 25 with a low (<25%) emphysema percentage. Because a limited number of subjects had a high percentage of emphysema on CT scan, all meeting the criterion of 25% or higher were included in our study (n = 25). Then, subjects with <25% emphysema on CT scan were selected by consecutive sampling from a list ordered by ascending emphysema percentage (ie, selected subject 1 was number 2 in the list, selected subject 2 was number 5, and so on) until to complete 25 subjects. This was done to ensure that the population with low emphysema was equally distributed across this range of interest.

Imaging Assessment

CT image acquisition was performed according to the LTRC protocol described elsewhere. Emphysema was defined as low attenuation areas below −950 Hounsfield units (HU). Quantitative measures of emphysema for both the whole lung and for the upper, middle, and lower one-thirds were performed by using open-source software (www.airwayinspector.org). Unless otherwise specified, whole-lung emphysema determined by CT scan is referred to as emphysema. The thirds were defined as equal divisions of the total lung volume. The total lung volume on CT scan was measured at full inspiration and reported as total lung capacity (TLC).

The CT images were visually inspected using a window width of 1000 HU and a level of −500 HU. RB1 was identified and its segmental bronchus designated as a third airway generation (AG). RB1 was selected based on both prior investigation and its general perpendicular orientation to the CT scanning plane. From that segmental bronchus, detailed slice-by-slice examination of CT regionally interpolated images was performed to identify and count its daughter branches based on Weibel’s model of airway anatomy. The expected number of daughter branches was calculated by the equation \( n = \frac{2}{e} \) where \( n \) is the AG of interest, starting in the third AG where \( n \) was considered to be 0. Based on the assumption that all subjects would have the same number of daughter branches in the third AG, fourth AG, and fifth AG, the airway dropout was summarized as the total airway count (TAC) of the branches from the sixth AG to the eighth AG. Twenty CT scans were assessed independently following the above method a second time 1 month later by the first reader and by a second reader to assess the intra- and interreader reproducibility of the airway counts.

Clinical and Physiologic Assessments

Dyspnea was measured by using the modified Medical Research Council (mMRC) score. All subjects underwent standardized spirometry, single-breath diffusing capacity for carbon monoxide (DLco), and 6-min walk distance (6MWD) testing. The post-bronchodilator FEV1, FVC, and DLco are expressed as percentages of predicted values using standardized prediction equations. Each subject’s BODE index was also calculated.

Statistical Analysis

The intra- and interreader reproducibility of airway counts was conducted using the intraclass correlation coefficient and Blom-Altman analysis. Comparisons between baseline characteristics of subjects with <23% and ≥25% emphysema were performed using t tests and \( \chi^2 \) tests. Correlation and linear regression analysis was used to assess the relationship between TAC and emphysema. Pairwise relationships of TAC with clinical and physiologic variables and with BODE index were assessed via Pearson correlation coefficients. Furthermore, we assessed the ability of TAC to predict a categorized BODE (≥7 vs <7 points) through logistic regressions. BODE is a validated summary index of several clinical predictors of COPD to predict mortality. A BODE score of 7 or higher predicts the...
Results

Reliability of Airway Counts

The intra- and interreader reproducibility of airway counts was high, as suggested by the intraclass correlation coefficients. The intraclass correlation coefficients for the TAC and the individual sixth AG, seventh AG, and eight AG were 0.98, 0.85, 0.95, and 0.97 for the intrareader assessments and 0.97, 0.75, 0.90, and 0.86 for the interreader assessments, respectively (Fig 2).

Population Description

Baseline characteristics of the 50 subjects by emphysema groups are shown in Table 1. Subjects with ≥25% emphysema were significantly younger, had a higher mMRC dyspnea score, TLC, and BODE index, lower FEV₁% predicted and DLCO% predicted, and shorter 6MWD than their counterparts with <25% emphysema. There were no differences between subjects’ characteristics (except for TLC) as a function of the brand of CT scanner (Table 2).

Total and Generational Airway Counts

Those subjects with ≥25% emphysema had a lower TAC (18.5 ± 10.2) than those with <25% emphysema (29.8 ± 11.3) and the differences were statistically significant (P = .0005) (Fig 3). After adjustment for age, gender (female = 1), BMI, and TLC, the mean TACs for the high and low emphysema groups were 19.3 and 29.0, respectively (P model < .0001). This difference in airway count between the two emphysema groups was also noted when analyzing the sixth AG (6.4 ± 2.2 vs 7.5 ± 1.2, P = .03), seventh AG...
Relationships Among Airway Counts, Clinical and Physiologic Variables, and BODE Index

Airway counts were correlated with dyspnea, FEV₁% predicted, DLCO% predicted, exercise capacity, and BODE index, which are known to have prognostic value in subjects with COPD. Correlations of TAC and generational airway counts were stronger with BODE index than with mMRC dyspnea score, FEV₁% predicted, DLCO% predicted, and 6MWD (Table 3). Those subjects with lower TAC had a higher mMRC dyspnea score and BODE index, and a lower FEV₁% predicted, DLCO% predicted, and 6MWD.

Predictive Ability of TAC for BODE

TAC was a good predictor of a high (worse) BODE index, as suggested by the area under the ROC curve of TAC: 0.84 (95% CI, 0.73-0.95) (Fig 5). TAC (mean ± SD, 14.9 ± 8.5 airways) for subjects with BODE ≥ 7 points was statistically significantly lower than for subjects with BODE < 7 (28.9 ± 10.9 airways, P < .0001).

Data are presented as mean (SD), except for male gender and BODE index categories, which are expressed as No. (%). P values were computed with the t test or χ² test (or the Fisher exact test). CT scan slice thicknesses of the Siemens and GE scanners were 1.25 mm and 1 mm, respectively, with 50% overlap. More details about the CT imaging protocol are in Han et al. 6 GE = General Electric; RB1 = apical bronchus of right upper lobe. See Table 1 legend for expansion of other abbreviations.

The postbronchodilator FEV₁% predicted and FEV₁/FVC ratio data are missed for one subject. The BODE index for this subject was computed with his prebronchodilator FEV₁% predicted of 86%.
In this study of a subset of subjects enrolled in the LTRC, we performed a detailed visual assessment of the third through eighth AG arising from the RB1. There was an inverse association among the TAC, the airway count of the sixth AG to the eighth AG of RB1, and emphysema. Although TAC and airway counts of the sixth AG to the eighth AG were directly related to both spirometric measures of lung function and the distance walked by a subject in 6 min, they were inversely related to both mMRC dyspnea score and BODE index. A subsequent regression analysis showed that TAC was a predictor of a high (worse) BODE index.

TAC-Emphysema Association

To our knowledge, there are data only on airway branch counts on clinical CT scans of smokers with normal lung function but not on smokers with emphysema.\(^8\) In the cohort reported here, we found an inverse association between TAC and emphysema and its physiologic surrogate, DLCO. Those subjects with \(>25\%\) emphysema had significantly lower TAC and generational airway counts than those subjects with \(<25\%\) emphysema. This finding is in agreement with an early study by Scott and Steiner,\(^29\) which reported a decrease in macroscopic airway count by bronchography with tantalum in subjects with a high emphysema percentage measured by histologic means compared with those with a low emphysema percentage. Later, Montaudon et al.\(^8\) reported that there were no differences in the total and generational airway counts visible on CT scans between smokers and nonsmokers with normal lung function. Although emphysema was not reported in that study, we speculate that they may have not observed differences in the airway count because their smoking cohort did not have significant emphysema.

TAC-Association With Clinical Variables and Ability to Predict BODE Index

There is little information regarding the clinical relevance of proximal airway count. In this study, pairwise correlation analysis showed that the total count of visible airways was associated directly with FEV\(_1\)% predicted, DLCO% predicted, and 6MWD, and was associated inversely with mMRC dyspnea score and BODE index. The observed association between lung function and airway count is in agreement with a similar finding reported by Leader et al.\(^30\) They used the airway count section (not the generational airway count) and found an association between this CT imaging metric and the magnitude of the FEV\(_1\) decrement. Although the association between emphysema, dyspnea, exercise capacity, and BODE...
Study Limitations

This study has some limitations. First, this was a convenience sample from the LTRC initiative selected to represent the breadth of emphysema seen in clinical practice. Furthermore, there is inherent selection bias because subjects were enrolled before undergoing either surgical treatment or diagnosis for their condition (COPD, interstitial lung diseases, and others). Hence, they may not be fully representative of all smokers. However, the differences found between the two emphysema groups are similar to those reported by others. 31

Second, the study lacks histopathologic corroboration. The apparent pruning of the proximal airway tree we observed may have been due to the distortion and collapse of the airways related to the change in tissue properties associated with emphysema, rather than the outright absence of airways as observed by Hogg et al. 7 Although this is certainly possible, the airways surveyed in our study were the more central cartilaginous bronchi and sufficient distortion to render them invisible seems unlikely. Additionally, the increase in contrast between low attenuating areas of emphysema and an adjacent airway may, to a degree, mitigate this phenomenon by enhancing structure visibility.

Third, the airway count was performed manually on a slice-by-slice basis and not in a volumetric reconstruction of the airway tree. Although this two-dimensional approach may lead to confusion regarding the ascertainment of local AG, such manual methods have been employed previously as a standard reference to validate more automated software-based analysis of the airways. 32 To further support our method, the intra- and interreader agreement in the TAC was high.

Fourth, the presence of visually apparent emphysema on the CT scan may bias the reader to underreport TAC. We did not find, however, that the differences in airway count between the two readings were associated with emphysema percentage (data not shown).

Finally, we assumed that the airway count of RB1 was representative of the distribution of airway count through the whole lung. It may be that such an assumption is not appropriate because it has been shown that

Table 3—Pearson Correlation Coefficients (r) Between Airway Counts of RB1, Dyspnea Score, Lung Function, 6MWD, and BODE Index in 50 Subjects

<table>
<thead>
<tr>
<th>Airway Counts of RB1</th>
<th>mMRC Dyspnea Score</th>
<th>FEV1% Predicted</th>
<th>DLCO % Predicted</th>
<th>TLC, L</th>
<th>6MWD, m</th>
<th>BODE Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total airway count (generations 6-8)</td>
<td>−0.42</td>
<td>0.52</td>
<td>0.45</td>
<td>−0.01</td>
<td>0.36</td>
<td>−0.55</td>
</tr>
<tr>
<td>Sixth generation</td>
<td>−0.30</td>
<td>0.34</td>
<td>0.36</td>
<td>0.13</td>
<td>0.39</td>
<td>−0.45</td>
</tr>
<tr>
<td>Seventh generation</td>
<td>−0.41</td>
<td>0.45</td>
<td>0.43</td>
<td>−0.04</td>
<td>0.38</td>
<td>−0.53</td>
</tr>
<tr>
<td>Eighth generation</td>
<td>−0.40</td>
<td>0.53</td>
<td>0.43</td>
<td>−0.03</td>
<td>0.28</td>
<td>−0.50</td>
</tr>
</tbody>
</table>

*P* < .05 for all correlations, except for all TLC correlations, which were not significant. See Table 1 and 2 legends for expansion of abbreviations.
there are regional variations in airway morphometry on CT scan. Further investigation is needed to clarify airway count distribution by lung lobes by means of CT scanning.

**CONCLUSIONS**

In summary, the total CT imaging-based count of airways present in the sixth through eighth AG (TAC) of a subset of smokers enrolled in the LTRC was inversely related to densitometric measures of emphysema and was also a predictor of a high BODE index. This latter observation suggests that CT imaging airway count may be a unique COPD-related clinically relevant phenotype. Additional investigation is needed in a larger sample to further explore the clinical significance of emphysema-associated pruning of the airway tree and to validate its use as a CT imaging phenotype of lung disease in smokers. Software development to reconstruct the bronchial tree and count airway branches by generation with high accuracy and reproducibility is desirable.

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Dr San José Estépar: contributed to software development, which allowed the CT imaging analysis of emphysema, and to the writing and final approval of the manuscript.
Mr Ross: contributed to software development, which allowed the CT imaging analysis of emphysema, and to the writing and final approval of the manuscript.
Dr Matsuoka: contributed to the writing and final approval of the manuscript.
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Dr Silverman: contributed to the writing and final approval of the manuscript.
Dr Washko: contributed to the writing and final approval of the manuscript.

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**REFERENCES**