Computed Tomographic Airway Morphology in Chronic Obstructive Pulmonary Disease

Remodeling or Innate Anatomy?

Alejandro A. Diaz[1], Raul San José Estépar[2], and George R. Washko[1]

[1]Division of Pulmonary and Critical Care Medicine, and [2]Surgical Planning Laboratory, Laboratory of Mathematics in Imaging, and Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Abstract

Computed tomographic measures of central airway morphology have been used in clinical, epidemiologic, and genetic investigation as an inference of the presence and severity of small-airway disease in smokers. Although several association studies have brought us to believe that these computed tomographic measures reflect airway remodeling, a careful review of such data and more recent evidence may reveal underappreciated complexity to these measures and limitations that prompt us to question that belief. This Perspective offers a review of seminal papers and alternative explanations of their data in the light of more recent evidence. The relationships between airway morphology and lung function are observed in subjects who never smoked, implying that native airway structure indeed contributes to lung function; computed tomographic measures of central airways such as wall area, lumen area, and total bronchial area are smaller in smokers with chronic obstructive pulmonary disease versus those without chronic obstructive pulmonary disease; and the airways are smaller as disease severity increases. The observations suggest that (*1*) native airway morphology likely contributes to the relationships between computed tomographic measures of airways and lung function; and (*2*) the presence of smaller airways in those with chronic obstructive pulmonary disease versus those without chronic obstructive pulmonary disease as well as their decrease with disease severity suggests that smokers with chronic obstructive pulmonary disease may simply have smaller airways to begin with, which put them at greater risk for the development of smoking-related disease.

Keywords: wall area percent; wall thickness; wall area; lumen area; branching generation number

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Correspondence and requests for reprints should be addressed to Alejandro Diaz, M.D., M.P.H., Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. E-mail: adiaz6@partners.org

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Expiratory airflow obstruction in chronic obstructive pulmonary disease (COPD) is due to a combination of emphysematous destruction of the lung parenchyma and remodeling of the small airways (1). Although the contribution of the latter to airflow resistance was documented by retrograde catheterization in the 1960s (2), their size precludes direct radiologic observation and it was not until the mid-1990s that a link was made between these structures and the central cartilaginous airways visible on computed tomographic (CT) scan.

Using explanted lung lobes from 72 subjects, Tiddens and colleagues (3) found that thickening of the inner wall area (WAi: bounded on the luminal side by the basement membrane and extending outward to the outer edge of the smooth muscle layer; Figure 1) was associated with reductions in maximal expiratory flow and the FEV_1/FVC ratio. It was also observed to be proportionally greater in the smaller airways and was associated with peripheral membranous airway inflammation. This correlation between central airway morphology and lung function as well as the possible similarities between cartilaginous airway remodeling and small-airway inflammation provided an opportunity for the imaging community to leverage CT scanning in clinical investigation. One of the first groups to do so focused on the apical segment of the right upper lobe.

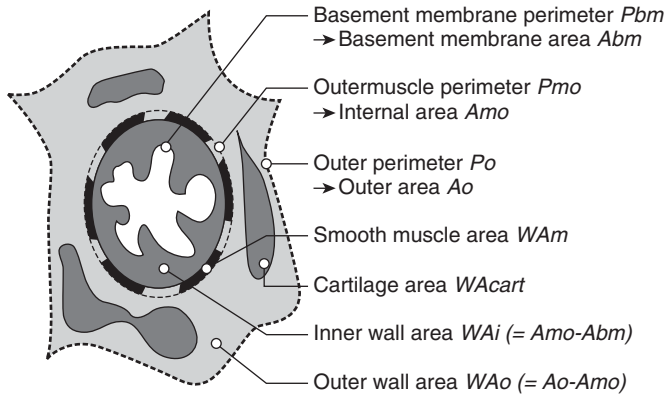

Figure 1. Artist's rendition of prototypic airway components. Reprinted by permission from Reference 3.

Nakano and colleagues collected CT and lung function data on 114 smokers and performed objective assessments of the lumen area (Ai), wall area (WA), total bronchial area (Ao: Ai + WA), and the wall area percent [WA%: 100 × WA/(WA + Ai)] (4). Those with the greatest expiratory airflow obstruction had the smallest airway Ai and the greatest WA%. The latter association persisted even after adjusting for the amount of objectively detected emphysema evident on CT. Measures of WA% obtained from the apical segment of the right upper lobe were also highly correlated with similar measures at other sites in the lung, suggesting a self-similarity in tracheobronchial tree structure.

In 2005 Nakano and colleagues further provided compelling evidence that central airway structure as assessed by CT scan provides insight into the morphology of the distal small airways (5). They did this by examining the preoperative CT scans of 22 smokers undergoing lung resection for suspected malignancy. Using a technique adapted from histopathologic investigation, they plotted the square root of the wall area (y axis) versus the perimeter of the lumen (Figure 2). The clear graphical association between CT and histology provided the final piece of the foundation supporting the assumption that the central airway morphology of smokers provides insight into distal small-airway remodeling.

Wall thickening and lumen narrowing are critical components of small-airway disease (6). These airway changes reflect a mural remodeling or repair process and a deposit of inflammatory mucous exudates. There are, however, more limited histopathologic data on central airway wall thickening and encroachment into the lumen. The most notable of these works, by Tiddens and colleagues, was presented previously. Below we argue that current evidence shows that in addition to airway remodeling, there are another two contributors to CT lumen dimension: native airway structure and loss of surrounding parenchymal integrity.

Data Reconsidered

When referring back to the histopathologic work by Tiddens and colleagues (3) there was indeed evidence of cartilaginous airway wall thickening (WT) proportionate to decrements in the FEV_1/FVC ratio. The WAi ranged from 0.25 to 9 mm^2 and, based on the regression data provided in the manuscript, a subject with an FEV_1/FVC ratio 40% of predicted (*solid line* in Figure 3) would have a WAi that is approximately 0.2 mm^2 greater in area than an airway with the same basement membrane perimeter taken from a subject whose FEV_1/FVC ratio is twice that value (*dashed line* in Figure 3). Although readily detectable on histopathologic evaluation, this airway WT is, however, small in scale and likely beyond the resolution of current clinical CT scanning algorithms. For example, Donohue and colleagues (7) demonstrated that a modest increase in CT WT of proximal airways was associated with greater cumulative pack-years of smoking (0.002 mm per 10 pack-years of smoking) (7), highlighting the small scale of such a change in WT and the complexity of interpreting its meaning. In addition to the limited CT resolution, the variety of airway algorithms and software used as well as the lack of standardized methods for airway measurement adds to the complexity of the imaging assessment of the bronchi (8). A detailed discussion of these issues is, however, beyond the scope of this Perspective.

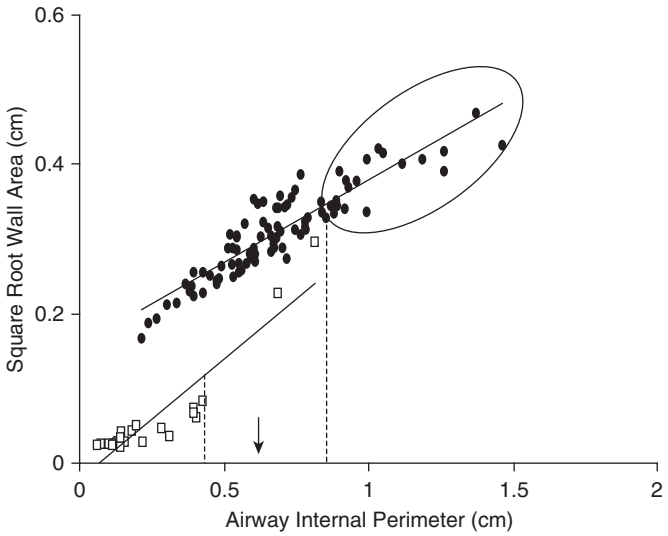

Figure 2. Histopathologic (*open squares*) and computed tomography–based (*solid circles*) assessments of the relationship of the square root of wall area versus airway internal perimeter. *Long vertical dashed line* = the Pi cutoff used for CT (0.75 cm). The mean wall area percentage (WA%) for all airways more than this threshold (*encircled by a solid line*) was compared with the histologic measurement of Aaw at a Pi of 4 mm (*short vertical dashed line*). A *downward-facing arrow* references the point at which airways are at a diameter of 2 mm. Reprinted by permission from Reference 5.

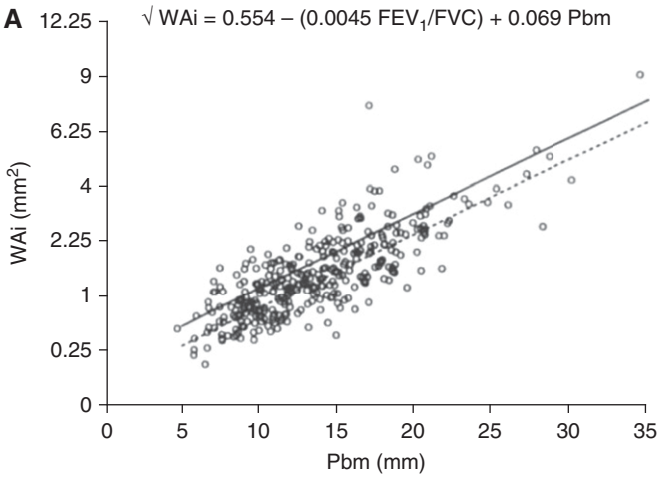

Figure 3. Relationship of airway inner wall area (WAi) versus airway basement membrane perimeter (Pbm). The *solid line* represents values for a subject with an FEV_1/FVC ratio 40% of predicted, and the *dashed line* represents values for a subject with an FEV_1/FVC ratio 80% of predicted. Reprinted by permission from Reference 3.

In referring back to data presented by Nakano and colleagues (4), subjects with a smaller lumen area or greater ratio of wall to total bronchial area had more severe expiratory airflow obstruction. Interestingly, those with a greater total bronchial area (Ao) also tended to have a higher FEV_1%, although the latter did not reach statistical significance. This first report of a potentially direct (but statistically insignificant) relationship between airway size and lung function would suggest (and was later confirmed) that smokers with greater expiratory airflow obstruction have smaller airways with smaller lumens and smaller wall areas. The increase in WA% is simply due to a disproportionate decrease in lumen area compared with wall area.

We examined series of CT scans obtained in smokers with and without COPD as well as in a cohort of never-smokers who had no evidence of respiratory disease (9). Smokers with lower expiratory airflow (lower FEV_1%) indeed had increased central airway WA%, but on closer inspection they had smaller lumen, wall, and total bronchial areas. These findings have since been replicated by Smith and colleagues, who demonstrated that in anatomically matched airways subjects with COPD (vs. non-COPD) have smaller lumen and wall areas (10). The aggregate of these data suggests that subjects with more severe COPD have smaller central airways.

These radiologic observations may explain the associations between the CT-derived WA% and lung function, but how to reconcile this to the previous link created between CT and histopathology? The median FEV_1 in those 22 subjects was 85% predicted and the median FEV_1/FVC ratio was 74% predicted (5). These were a cohort of smokers, but they were predominantly a cohort of smokers with normal lung function. Intrinsic bronchial anatomy may be largely responsible for the morphologic associations observed between the proximal and distal airways.

Have we also been fooled, however, by the simplicity of our airway analysis? The airways are not a static structure. They are distensible tubes whose morphology is influenced by the properties of the elastic matrix in which they reside. For example, disruptions of parenchymal interdependence due to emphysema may result in incompletely expanded airways with lung inflation while fibrotic parenchyma with increased elastic recoil may result in traction bronchiectasis. Emphysema with hyperinflation may, however, have competing effects (11). If volume dominates, the airways will be dilated and the WA% decreased, but if parenchymal disruption dominates, the airways will be incompletely dilated and the WA% will be increased (Figure 4). Such radial and longitudinal distortion of the airways will result in under- or overestimates of a "true" WA%. A solution to this issue may be found in measures of airway volume.

There is a respirophasic nature to airway morphology, in which inflation results in airway dilation and a decrease in WA% and deflation results in reductions of airway caliber and increases in the WA%. This airway deformation is not, however, associated with a cyclic gain and loss of mural tissue. For this reason, airway wall volume may be a more accurate assessment of mural tissue than the WA% or measures of wall thickness.

We calculated the wall volume (WA × segmental length between branch points) of several intra- and extraparenchymal airways in healthy never-smokers (12). Those never-smokers with lower FEV_1% had smaller wall volumes. In a similar exercise in smokers, those with COPD also had smaller wall volumes and the linear correlations between wall volume and the FEV_1% were similar to what was observed in the healthy never-smokers (Figure 5). Again, smokers with greater expiratory airflow obstruction had smaller airway wall volumes.

One study has shown that subjects who had smaller lungs as measured by FEV_1 (and potentially smaller airways) were more likely to develop COPD regardless of smoking exposure (13). If we presume that much of what is being measured on CT is innate airway structure, why wouldn't all smokers of smaller stature with smaller lungs (and therefore presumably smaller airways) be at greater risk for the development of COPD? An answer to that question may be found in a series of publications that first appeared more than 40 years ago.

In 1974 Green, Mead, and Turner (14) were exploring the maximal expiratory flow–volume relationships in subjects without lung disease and found that the large degree of variability of these measures could not be explained by lung size alone. The unpredictability of these measures was due, rather, to the variable morphology of the tracheobronchial tree. The dysanaptic or unequal development of the components of the organ of interest would lead to disproportionately large airways for a given lung volume. One may then infer that those with disproportionately small airways would in turn be more susceptible to the development of COPD. Although this theoretical work was largely built on a physiological basis, more recent CT data have substantiated its existence.

Nishimura and colleagues (15) demonstrated that the offspring of subjects with COPD (vs. control subjects) had a lower ratio of tracheal cross-sectional area

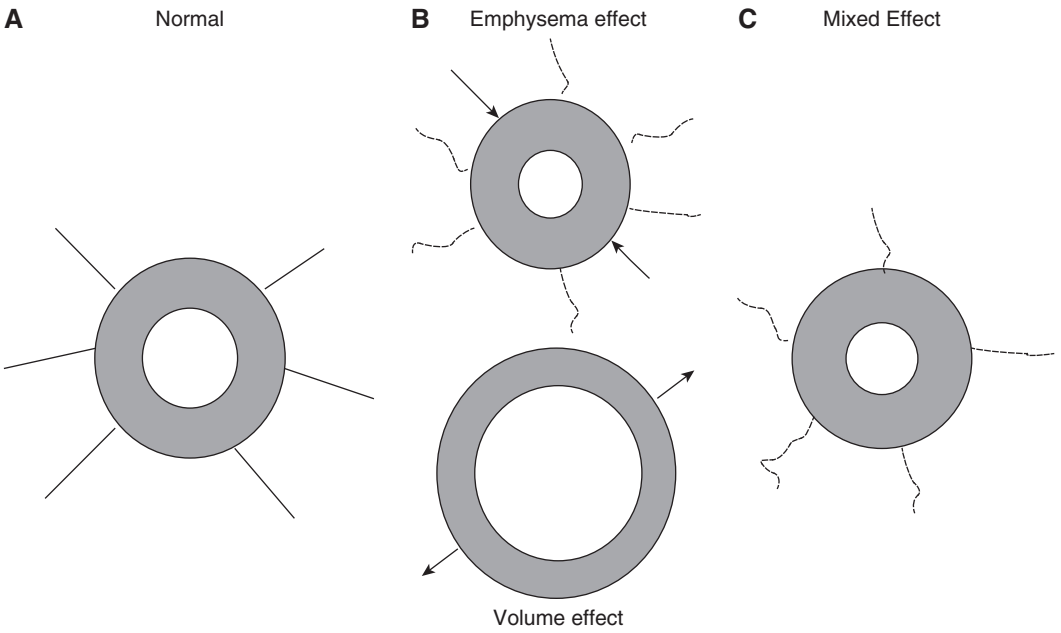

Figure 4. Illustration of the conflicting effects of emphysema and lung volume on airway dimensions. (*A*) Intact airway with attachments to the lung parenchyma. (*B*) *Top*: Lung attachments are broken by emphysematous destruction, resulting in a diminished total bronchial area (Ao; indicated by the *arrows*) and increased wall area percent (WA%; *gray area*). *Bottom*: An increase in lung volume results in increased Ao (indicated by the *arrows*) and lower WA%. (*C*) The likely result of these two processes is an airway with lower Ao and increased WA% compared with a normal airway. Reprinted by permission from Reference 11.

to vital capacity, a measure of dysanapsis, than the offspring of non-COPD control subjects. They went on to hypothesize that the heritability of airway size "may partly explain the susceptibility to the future development of COPD." Later, Patel and colleagues (16) demonstrated that airway thickening showed independent aggregation within families of patients with COPD, supporting a potential link between intrinsic lung structure and the risk of developing disease. Additional

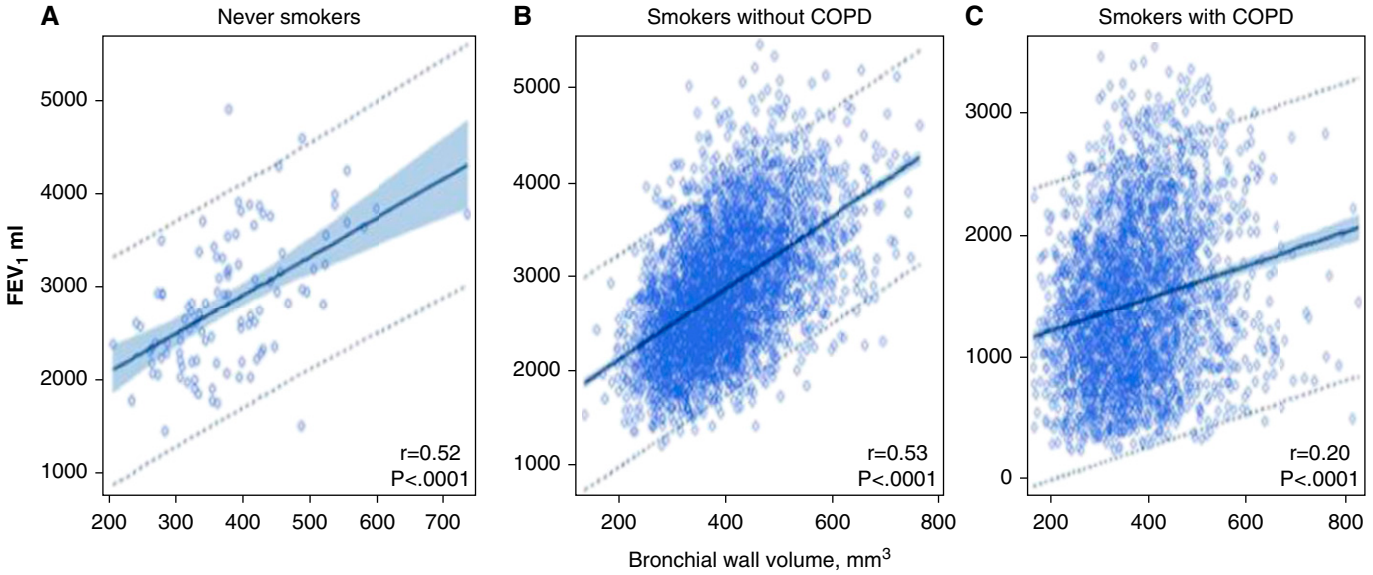

Figure 5. Relationship of FEV_1 and bronchial wall volume in (*A*) never-smokers, (*B*) smokers without chronic obstructive pulmonary disease (COPD), and (*C*) smokers with COPD. Plots of *B* and *C* were constructed with data from 3,471 (mean age, 57 yr; female, 45%; non-Hispanic white, 61%; current smoker, 59%) and 2,347 (mean age, 64 yr; female, 40%; non-Hispanic white, 81%; current smoker, 42%) participants in the COPDGene study, respectively, who had complete data on bronchial length. The *shadow area* represents the 95% CI of the regression (*solid lines*), and the *dotted lines* indicate the 95% prediction limits. [For visual purposes, the plot in *A* is slightly modified by permission from that of Reference 12.]

corroborative data supporting the concept of dysanaptic lung development include the observed association between decreased expiratory airflows in healthy women during exercise (17), people living at altitude (18), and subjects with asthma (19–21).

A final aspect of quantitative CT airway analysis that must be mentioned is the influence of the airway generation on the strength of the correlations between these measures and lung function. Hasegawa and colleagues (22) studied 52 patients with clinically stable COPD and found that the WA% was inversely related to the FEV_1% and that the strength of this association increased with more distal assessments of airway morphology. The regression coefficients for the association between WA% and the FEV_1% trended from –0.224 for the third generation to –0.552 for the sixth airway generation measures. These results and those reported in a subsequent investigation using optical coherence tomography (23) strongly suggest that the trend in these associations is not a phenomenon that can be ascribed to limited CT resolution and image noise. A straightforward explanation is that measures obtained from more distal aspects of the bronchial tree provide better estimates of the small airways thought to be most responsible for the spirometric impairments we observe clinically.

If central airway morphology provides only limited information about mural remodeling in smokers, how can one leverage such data to increase our understanding of COPD? One potential application may be in an investigation of disease susceptibility. Several large observational studies such as the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) (24) and COPDGene (25) have reported that the median pack-year tobacco history is similar across GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages of COPD, an observation contrary to an assumption that susceptibility to lung injury is uniform in all smokers. Susceptibility may be explained by variable inflammatory response to noxious gas or particulates and, although it has not been explored, such susceptibility may also be explained in part by distal lung anatomy inferred from central airway structure.

If one assumes that the airways are a self-similar dichotomously branching structure whose rate of tapering in caliber is fairly consistent from parent to daughter (i.e., third to fourth or fourth to fifth generation, etc.), then the number of airway generations (branching generation number, BGN) between a selected central airway and its 2-mm lumen diameter descendant can be calculated. Mathematically, the projected BGN = [ln (3.14/subsegmental lumen area) + K]/ln (LA ratio), where the LA ratio is the ratio of lumen area daughter to parent airway (e.g., subsegmental LA/segmental LA), and K is a constant representing the most distal airway measure. Using LA ratios based on our data (12) and those of Weibel and Gomez (26), Mauroy and colleagues (27), and Montaudon and colleagues (28), there was a high degree of concordance between estimated BGNs in these models and in multivariable regression analysis highly statistically significant direct relationships between the BNG and measures of peak expiratory airflow.

On the basis of the assumption that the airways are a dichotomously branching network (29), a subject will have 2^n small airways, where n is the BGN. A subject with a BGN of 10 will have 2^{10} or 1,024 2-mm lumen diameter airways whereas a subject with a BGN of 12 will have 2^{12} or 4,096 small airways. Resistance to airflow is proportional to the fourth or fifth power of airway lumen radius along any selected pathway, but when considered in the context of a network of airways the lung resistance is also determined by the number of parallel pathways (30). Those with a smaller number of parallel pathways (lower BGN) will have greater innate resistance to airflow and, for an identical inflammatory response, will have a proportionally greater increase in airway resistance than a subject with a higher BGN. The predilection to develop COPD would therefore not be predominantly due to the rate of decline in expiratory airflow but might depend on two other elements: first, the lung function reached at peak health (approximately at 25–30 yr of age), and second, susceptibility to developing increased airway resistance because of reduced numbers of parallel airway pathways. Note that the theoretical branching generation number is determined by assuming that the airway tree is intact and provides an estimated number of bronchial generations to reach a targeted airway size. However, it may not be an appropriate model to predict airway dropout, which is thought to contribute to the development of airflow obstruction in smokers (30).

Unambiguous evidence indicates that there is central airway remodeling in smokers. We do not discount this evidence but rather urge caution in associating central airway morphology with remodeling in smokers. Central airway morphology on CT scan is an aggregate of innate structure, distensibility, properties of the surrounding tissue matrix, and inflammation of the airway wall. The relative contributions of each may vary by individual and may even vary over time. This does not devalue the contributions that CT can make to the assessments of airway morphology in smokers, nor does it discount prior investigations demonstrating compelling clinical associations. These findings are real, but the correlation coefficients reported in the literature belie the complexity of the endotype.

Future Directions

The breadth of potential future directions for the application of imaging to chronic lung disease is large. These include improvements in image resolution at lower radiation doses, advances in more invasive technologies such as optical coherence tomography, and greater attention to the reproducibility of such measures (i.e., the importance of lung volume in longitudinal analysis). We believe these improvements will help to answer questions related to lung structure, such as the following: What are the structural features in the lung that may mitigate/increase susceptibility to injury from chronic tobacco smoke exposure? Can airway structure in youth predict the development of COPD at older age? How can we use these data to prevent disease? Although more abstract than the technological innovations sure to come in imaging, preventing disease may have the greatest impact on community health. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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