Quantitative Computed Tomography Assessment of Airway Wall Dimensions

Current Status and Potential Applications for Phenotyping Chronic Obstructive Pulmonary Disease

Harvey O. Coxson¹

¹Department of Radiology, Vancouver General Hospital, The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, University of British Columbia, Providence Heart + Lung Institute, St. Paul's Hospital, Vancouver, British Columbia, Canada

Airway remodeling is extremely important in the pathophysiology of chronic obstructive pulmonary disease (COPD). Since the site and nature of airflow obstruction was described by Hogg, Thurlbeck, and Macklem, investigators have been looking for methods to non-invasively measure the airway wall dimensions in subjects with and at risk for COPD. The advent and proliferation of computed tomography (CT) initially allowed investigators to quantify changes in lung parenchymal structure in subjects with emphysema, and more recently attention has turned to the measurement of airway wall dimensions. Unfortunately, while the lung density is relatively easy to quantify, reliable airway measurements have proven to be more difficult to obtain. However, recent advances in CT technology and new computer algorithms have changed the way investigators have measured airways using CT, and it is now hoped that many of the early issues surrounding airway measurements can be resolved. The measurement of airway wall dimensions is important because it is well known that chronic airflow limitation can be caused by a combination of airway and parenchymal changes. The phenotypic expression of these different subtypes of COPD is vital because a therapy designed to modulate the inflammation in airways may be contraindicated in subjects with the emphysema phenotype and *visa versa*. Therefore, these new imaging techniques are very likely to play a front-line role in the study of COPD and will, hopefully, allow clinicians to phenotype individuals, thereby personalizing their treatment.

Keywords: computed tomography; airways; emphysema; chronic obstructive pulmonary disease

It is well recognized that chronic obstructive pulmonary disease (COPD) is a collection of conditions that ultimately result in chronic airflow limitation. It is also well recognized that while the actual mechanisms that lead to the airflow limitation are diverse, the underlying cause is inflammation, which in susceptible individuals leads to remodeling of the lung either through destruction of the lung parenchyma (emphysema) or airway wall changes, leading to airway obstruction. The purpose of this article is to review some of the new techniques that have been developed to noninvasively measure airway wall dimensions. The second part of the review will cover how these airway techniques, in combination with computed tomography (CT)

assessments of emphysema, can hopefully allow clinicians to subcategorize subjects in groups of individuals whose airflow limitation is caused by similar pathogenic mechanisms. This is particularly important, because if the airway and emphysema manifestation of COPD are under genetic control, a therapy designed to modulate the inflammation in airways may be contraindicated in subjects with the emphysema phenotype and *visa versa*.

AIRWAY ANALYSIS

Studies of airway remodeling have consistently shown that small airways (< 2 mm in diameter) are the site of the major airflow limitation in COPD (1, 2). Imaging of the lung using CT technology produces an image of the lung that is similar to that seen on gross pathology and provides a noninvasive method to study these airways. This technique should provide a great step forward from traditional pathology because it may provide a method to both understand the pathogenesis of the disease process and to study the effect of therapeutic interventions. The selection of subjects for interventional studies is extremely important for studies such as those involving surgical resection of lung tissue (lung volume reduction surgery) (3, 4) or studies involving subjects with α_1 -antitrypsin deficiency in whom the disease is predominately emphysematous (5–9).

The initial studies of airway dimensions involved manually tracing the airway using the printed image. However, this process is not only very labor intensive and subject to large inter- and intraobserver error (10–12), but is also extremely dependent on the display parameters of the CT image. Investigators showed that the airway could only be accurately measured using a CT window level of –450 HU and a window width of 1,000 to 1,400 HU (10–13). While these images allow one to measure airways, they are not suitable for clinical uses, and since a printed version of the CT scan was the most common version of the CT images at that time, these images were rarely produced. The proliferation of computer algorithms that could read the CT scan data and analyze the X-ray attenuation values lead investigations into more automated methods to assess airway dimensions. In one of the first studies McNitt-Gray and coworkers found that the lumen area could be accurately measured using a threshold cutoff of –500 HU (14). King and coworkers followed up on these studies and refined the technique using excised formalin-fixed pig lungs, and showed that a threshold of –577 HU produced the least error in the measurements (15). However, of all the airway metrics, airway lumen was the easiest to obtain.

Airway wall dimensions, on the other hand, have proven to be much more difficult to obtain. There have been numerous algorithms developed over the years with the earliest and most simple of these techniques being the “Full-Width at Half Maximum” (“half-max”) method. Using this method, apparent X-ray attenuation values are measured along a ray projected from

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Correspondence and requests for reprints should be addressed to Harvey O. Coxson, Ph.D., Department of Radiology - Vancouver General Hospital, 855 West 12th Ave, Room 3350 JPN, Vancouver, BC, V5Z 1M9 Canada. E-mail: harvey.coxson@vch.ca

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a central point of the lumen to the parenchyma, and the distance between the point at which the attenuation is halfway between the local minimum in the lumen or parenchyma and the maximum within the wall is considered to be wall thickness (Figure 1) (16, 17). Unfortunately, the shape of this X-ray attenuation distribution curve is dependent on various parameters, including the reconstruction algorithm used to create the image, partial volume averaging due to field of view and orientation of the airway within the CT image, and the inevitable blurring of edges that occurs due to the point spread function of the CT scanner. Validation studies showed that this method overestimates airway wall area and underestimates lumen area, and that these errors become very large in small airways (16, 18). For these reasons investigators have developed numerous other algorithms to measure these airways, such as the "maximum-likelihood method," whereby the attenuation threshold along each ray is matched to an ideal calculated ray (18); the "score-guided erosion algorithm" (15), in which airway wall edges are found using an edge finding algorithm that assumes that airways are circular and have a relatively high density compared with the surrounding parenchyma; and an algorithm in which ellipses are fit to the airway lumen and wall (19).

While there is great interest in CT measurements of airway dimensions, the actual application of these techniques to the studies of COPD is still not widely used. One of the first and most influential studies of airway dimensions was an analysis of the right apical segmental bronchus by Nakano and colleagues (17). In their study, they showed that the percentage of the total airway (lumen plus wall) that was airway wall area (wall area percent [WA%]) correlated with the FEV₁, FVC, and the RV/TLC, but not the DL_{CO}. This is a surprising finding because the apical segmental bronchus is a large central airway and not a small airway, which has consistently been shown to be the site of airflow limitation (1, 2). Following up that study, Nakano and coworkers showed that there was a correlation between the WA% measured using CT and the wall area measured histologically in the same subjects, suggesting that while CT cannot be used to measure small airways, it can measure a process in the large airways that is a surrogate for the changes in the small airways (20). This is further backed up by other histologic data that shows that in subjects with COPD, there is a thickening of the airway wall in the large airways as well as the small airways (21). Other studies of large airways have shown that subjects with symptoms of chronic bronchitis have more airway wall thickening than subjects with airflow limitation and no symptoms (22, 23). Furthermore, recently Patel and coworkers have shown that there is a significant familial concordance of airway wall thickening such that if a subject with COPD has thickened airway walls, there is an increased odds ratio that his or her sibling(s) will also have airway wall thickening (23).

The advent of multi-detector row CT scanning has now allowed users to acquire thin slice contiguous images of the lung using a Z dimension that approaches that of the X-Y dimensions, although most studies still use CT slices with 1 to 1.25 mm slice thickness. If the CT images are acquired using 1 mm or less slice thickness, it is now possible for investigators to segment the airway tree in three dimensions, starting in the trachea and projecting out to the fifth or sixth generation (Figure 2). Furthermore, because the CT slices used to create this three-dimensional reconstruction are contiguous, it is also possible to reformat the airway tree into a single long tube that is sectioned in true cross-section of the central axis. Then, by applying advanced knowledge to the branching pattern of the airway tree, bronchial segments can be labeled so that investigators can know exactly where they are in the airway tree, which will allow them to the dimensions of a given airway between individuals or longitudinally (Figure 3) (24, 25).

Hasegawa and coworkers (25) recently compared measurements of the right apical and basal segmental bronchus at different branch points starting at the third generation to the sixth generation along its pathway. While their data did not show a correlation between the right apical segmental bronchus and FEV₁, their data did show that as they moved more distally, to the sixth generation of the airway tree, the correlation with FEV₁ improved. In a recent study, Coxson and colleagues compared airway wall measurements obtained using optical coherence tomography (OCT) to those obtained using CT (Figure 4) (26). OCT is a new bronchoscopic technique that uses near-infrared light in a manner similar to ultrasound to produce a two-dimensional image of the airway wall. In this study the authors used the knowledge of the OCT location at bronchoscopy to locate the exact airway region on three-dimensional reconstruction of the airway tree using CT. The findings of this study confirmed those of Hasegawa and coworkers, in that there was no correlation between airway wall dimensions and the segmental bronchi but there was in airways of the fifth generation (i.e., two more branch points distal from segmental bronchus), using either CT or OCT. These data suggest that these new three-dimensional techniques can be used to obtain measurements from a specific location within a specific airway and that these data may provide useful information about the airway wall structure in COPD.

As mentioned briefly above, there are numerous limitations to the use of CT scanning to measure airways. The first and obvious limitation is the resolution of the CT scanner. In usual clinical CT scanning the field of view limits the pixel size to approximately 0.5 mm in the X and Y dimension. Furthermore, until the recent advent of multi-slice CT scanners that can acquire images with 0.5 mm slice thickness, the CT slice thickness has limited the Z dimension to 1 mm. This means that the airways that are responsible for airflow limitation are below the resolution of the CT scanner. Second, there is no definitive data on the best algorithm to measure the airway wall. While a great deal of research has gone into airway wall algorithms (18–20, 24, 25, 27–30) there is no clear indication that one algorithm provides more useful data than another one. Third, the analysis of airways using three-dimensional algorithms is still in its infancy, and while there is great hope that these data will provide more meaningful data than the simple sample of two-dimensional airways, the data are clearly lacking in this area. An obvious problem of the three-dimensional approach is that there are now many airways that can be "named" and measured, and because this data has never existed before investigators do not know how many airways or how many airway paths to measure. It should also be noted that there are very few longitudinal studies of airways. Longitudinal analysis of airways is very problematic because the effect of CT image acquisition parameters such as X-ray dose, subject position, and volume of inspiration (to name a few) is completely unknown. It is very likely that the size of breath the subject takes will produce very different CT images of the airway tree, thereby effecting all of the data derived from the images. Finally, because airway measurements are still in their infancy and require specialized computer hardware and software, these analyses have a long way to go before they become practical in the clinical setting. As such, they remain in the research domain and are limited in their applicability.

PHENOTYPING OF COPD USING COMPUTED TOMOGRAPHY

Ever since the work by Hayhurst and coworkers (31), Gould and coworkers (32), and Müller and coworkers (33) showed that the extent of emphysema could be measured using CT, these techniques have been applied to studies of COPD. These early

Figure 1. This figure shows (A) the original computed tomography (CT) scan of a subject with a box around the airway of interest. (B) The rays demarcating the airway wall thickness are shown in an expanded view. The inside edge of the rays is defined as the halfway point between the low X-ray attenuation value in the airway lumen and the maximum X-ray attenuation value in the airway wall. The outer edge is defined as the halfway point between the maximum X-ray attenuation value of the wall the minimum X-ray attenuation value in the lung parenchyma. Rays that project into the neighboring blood vessel have been manually removed. Modified by permission from Reference 44.

studies showed that by using either a threshold technique whereby any lung voxels with X-ray attenuation values less than a given cutoff (e.g., -910 HU) (33) or the X-ray attenuation value (measured in HU) at a given percentile point of the distribution of X-ray attenuation values (e.g., 5th percentile point) (31, 32) correlated with extent of emphysema measured using quantitative pathology. These original studies have been refined over the years with different threshold points being redefined (9, 34, 35), as CT scanners and image reconstruction techniques have evolved but the basic principle remains the same, that low attenuating areas on CT are indicative of lung tissue destruction (Figure 5). Using these types of techniques, investigators have begun to group, or phenotype, individuals into different groups according to emphysema distribution (Figure 5) and airway wall thickness. In studies of lung volume reduction surgery, investigators showed that subjects with emphysema predominantly located in the upper, outer regions of the lung had a positive outcome, assessed using cardiopulmonary exercise ability, after surgery (36, 37). This study was corroborated by the National Emphysema Treatment Trial (NETT), which showed there was a survival advantage after surgery for those subjects with emphysema that was predominantly located in the upper regions of the lung (4). Other studies have looked at advanced “texture” features of the lung parenchyma to quantify structural changes in normal lungs, nondiseased smoker lungs, and lung from subjects with COPD (38, 39). These data suggest that smoking induces small changes in lung parenchyma that can be quantified. Furthermore, in the subjects who do advance to the emphysematous stage, not all emphysema is the same and the distribution phenotype may provide a survival advantage of the more diffuse forms of the disease.

Separating an individual on the distribution of emphysema is an easy example of phenotyping individuals, but investigators have also tried to separate subjects into the classical emphysema or airways disease phenotype. Nakano and colleagues first showed that both airway wall dimensions and extent of emphysema were independently associated with lung function (17). Furthermore, they also showed different aspects of pulmonary function related differently to airways (i.e., FVC) or emphysema (FEV_1/FVC , DL_{CO}), and that some subjects could be divided into an airway-predominant or emphysema-predominant phenotype (17, 40). Orlandi and coworkers examined subjects with COPD

and the clinical diagnosis of chronic bronchitis (22), and found that subjects with chronic bronchitis and COPD had thicker airway walls than those without chronic bronchitis and COPD (22). Berger and colleagues examined if airflow obstruction in

Figure 2. This figure shows a reconstruction of the airway tree with the surrounding lung parenchyma removed. The airway tree can clearly be seen starting from the trachea (generation 0) to at least the 5th generation airway. The airway tree was generated using Pulmonary Workstation 2.0 (VIDA Diagnostics Inc., Iowa City, IA).

Figure 3. This figure shows (A) a multi-planar reformat of the right apical segmental bronchus (RB1). The cross-section of the airway at the point of measurement is shown in B, while the path from the trachea is outlined in blue on the three-dimensional airway tree reconstruction in C and internal view of the three-dimensional reconstructed airway lumen is shown in D. The airway tree was generated using Pulmonary Workstation 2.0 (VIDA Diagnostics Inc.).

general was associated with thicker airway walls and showed that subjects with COPD had thicker airway walls than smokers or nonsmokers without COPD (41). A study by Aziz and coworkers used a combination of quantitative CT analysis, qualitative texture assessment, and qualitative airway analysis to assess the different morphologic features present in subjects with COPD (41). They conclude that the distribution of emphysema, centrally (core) versus peripherally (rind) and bronchial wall thickness have independent influences on airflow limitation and diffusion of gas (42). Recently, work by Patel and coworkers shows that the airway and emphysema phenotypes have a familial association such that subjects with airflow limitation and increased wall thickness had siblings with increased wall thickness and subjects with emphysema had siblings with increased extent of emphysema (23). These studies show that the measurement of emphy-

sema and airway wall dimensions are important in subjects with COPD because they may give insight into different pathogenic processes responsible for the disease and provide further evidence that this process is under genetic control. These techniques also provide mechanisms to sub-group subjects into different classes that may respond better to different therapeutic interventions such as lung volume reduction surgery (4, 36, 42, 43). However, none of the studies published to date show “excellent” correlations between lung function and CT measures of emphysema and airway wall remodeling. This is obviously because there are very few, if any, subjects with exclusively one simple phenotype. Most subjects have some form of overlap between airway wall changes and parenchymal destruction, so it remains a complicated task to phenotype individuals, but it is hoped that CT can provide a tool that will facilitate this important task.

Figure 4. This figure shows (A) a multi-planar reformat of the right lateral basal segmental bronchus (RB9). Panels B, C, and D are cross-section of the reconstructed airway, three-dimensional reconstruction of the airway tree, and the internal three-dimensional reconstruction view respectively as described in Figure 3. The optical coherence tomography images are shown in E and F, with the internal lumen marking and the lumen area (Ai) shown in E and the external boundary shown in F. The airway wall area (Aaw) would be the difference between the Ai in E and the total airway area in F. The airway tree was generated using Pulmonary Workstation 2.0 (VIDA Diagnostics Inc.). Panels A–D reprinted by permission from Reference 26. Panels E and F adapted by permission from Reference 26.

Figure 5. This figure shows a coronal view of the lung obtained using a multi-detector CT scan of the entire lung. (A) The low attenuation areas (< -950 HU) are highlighted using different colors for each lobe of the lung. (B and C) The three-dimensional spacing of these low attenuation areas are shown as colored blobs, and it can be seen that the distribution of these low atten-

uation areas can be quite different between individuals, with B showing extensive upper lobe distribution and C showing less extensive lower lobe distribution. These images were generated using Pulmonary Workstation 2.0 (VIDA Diagnostics Inc.).

CONCLUSIONS

It is generally accepted that COPD is a complex disease with complex interactions between genetics and environmental exposures. However, to fully understand this disease and hopefully develop new treatments the different manifestations, or phenotypes, of this disease must be fully understood. Noninvasive imaging such as CT imaging has provided a great deal of hope that with careful anatomic studies correlated with physiologic symptoms, the disease can be understood and subjects phenotyped into different disease classes.

Conflict of Interest Statement: H.O.C. received \$11,000 in 2005 and \$4,800 in 2006 and 2007 for serving on an Advisory Board for GlaxoSmithKline (GSK). In addition, he is the co-investigator on two multicenter studies sponsored by GSK and has received travel expenses to attend meetings related to the project. He 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 his salary between 2003 and 2006 (\$15,000/year) derives from contract funds provided to a colleague (Peter D. Paré) by GSK for the development of validated methods to measure emphysema and airway disease using computed tomography. There is no financial relationship between any industry and the current study.

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