Chairman's Summary

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BACKGROUND

Chronic obstructive pulmonary disease (COPD) is currently the 12th leading cause of disability in the world and is predicted to be 5th by the year 2020 (1). In the United States alone, it has been estimated that the annual cost of morbidity and early mortality due to COPD is approximately 4.7 billion dollars (2). COPD is a complex condition in which environmental factors interact with genetic susceptibility to cause disease. Tobacco smoke is the most important environmental risk factor, and in susceptible individuals it causes an exaggerated inflammatory response that ultimately destroys the lung parenchyma (emphysema) and/or increases airway resistance by remodeling of the airway wall (3). It has long been known that the pathway varies between individuals; some patients have predominant emphysema while others can have similar degrees of airflow obstruction due to severe small airway disease with relatively preserved parenchyma, but the proportion and contribution of each to the pathogenesis of disease is still unknown. Even though recent research has advanced our understanding of COPD pathogenesis, leading to the identification of potential targets and pathways for drug development, there are still major difficulties in conducting clinical trials designed to evaluate the benefits of new drug treatment for several reasons. These reasons include (*1*) the lack of validated short- and intermediate-term endpoints (or surrogates) that are predictive of future hard clinical outcomes, and (*2*) the lack of a method to provide precise phenotypes suitable for large-scale studies. It is for these reasons that computed tomography (CT) has become such an important tool in COPD research. CT provides a noninvasive method to obtain images of the lung that look similar to anatomic assessment, and CT images themselves are densitometry maps of the lung. Therefore any change in the structure of the lung will change the densitometry of the lung and, therefore, the image. Virtually every clinical center in all regions of the world has access to a CT scanner, so it is thought that CT images should be quite easy to obtain and it should be easy to conduct large, meaningful clinical studies.

However, while CT is a powerful tool, it does have some limitations and caveats for general use in clinical studies. These limitations include disagreements on the best method to analyze the lung parenchyma, no definitive study using airway wall algorithms, exposure of subjects to ionizing radiation, and the use of improperly calibrated CT scanners.

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In 2001 the Alpha-1 Foundation sponsored a workshop on the use of CT in longitudinal studies. That workshop resulted in recommendations on the use of CT to analyze the lung parenchyma, namely, the use of the lowest 15th percentile point of lung density (4). Since then there has been much debate surrounding CT analysis, and it was decided that another workshop was needed to readdress these issues. Specifically the workshop was designed to look at the use of CT for quantifying the lung parenchyma and the airway wall dimensions, and at how those methods could be applied to longitudinal studies and what drawbacks there may be in these approaches. This summary will only briefly discuss the broad concepts of these issues and deal specifically with the recommendations of the workshop.

CT STUDIES

The studies of lung parenchyma fall into three broad categories: (*1*) small cross-sectional studies conducted in a single institution, (*2*) large multi-institutional cross-sectional studies, and (*3*) longitudinal studies that may be either single-center or multicenter. Large multicenter studies are now becoming very popular as investigators try and use CT as a tool to phenotype individuals or to study disease progression or the effect of therapeutic interventions. There are, obviously, many factors to consider when designing studies that use CT, but the longitudinal multicenter studies are the most problematic because they include many different parameters that need to be standardized.

PARENCHYMAL ANALYSIS

The analysis of the lung parenchyma has essentially remained unchanged for 20 years. There are two features of the CT scan that are measured using quantitative methods: volume and the apparent X-ray attenuation. Volume is simply measured by separating, or segmenting, the lung from the surrounding chest wall and mediastinal structures. Once the lung is segmented, the computer is used to count the number of voxels within the lung and then multiply them by the voxel dimensions. The voxel dimensions in the X and Y plane are the field of view (FOV) divided by image matrix size (usually 512 $\times$ 512). The voxel dimension in the Z dimension is the slice thickness, or in the case of noncontiguous or "gapped" slices the distance between the two CT slices. Most lung segmentation algorithms are very robust at finding the lung, and there is uniform agreement that lung volume can be reliably and accurately estimated using CT scans. With the advent of MDCT scans, it is now possible to obtain contiguous thin slice images of the entire lung during a single breath-hold. This makes it possible to segment the individual lobes from each other so that in addition to lung volume it is now possible to obtain the volume of individual lobes (5–11). In the absence of contiguous thin slices, it may be still possible to manually segment the lobes by tracing the fissures using a cursor but this introduces a certain amount of error, although this is usually less than 10%.

The other metric that can be obtained from the CT scan is the apparent X-ray attenuation value. This value, measured in Hounsfield units (HU), gives an indication of the density of the lung, as the HU scale is directly proportional to density within

the biological range. Using this HU scale, Müller and coworkers (12, 13) originally reported that the percentage of the lung CT voxels that were less dense than the threshold cut-off value of −910 HU on conventional thick slice CT scans correlated with the extent of emphysema measured on pathological specimens. This study was reported at about the same time as another investigation by Hayhurst and colleagues (14, 15) showed that the lowest 5th percentile of the frequency distribution of X-ray attenuation values correlated with pathology. Over the succeeding years CT scanners have evolved to create thin slice images, then images acquired helically and then by multi-detector row. The latter two techniques have stood the test of time even though the actual value of either the threshold cutoff or the percentile values have been modified. The most common threshold point in use today is −950 HU (16), even though more recent data suggests that for multi-detector CT scanners −960 HU would be a better cutoff value (17). The percentile value has undergone some modification as well, and now the most universally used is the lowest 15th percentile cutoff value (4, 18–25). Numerous studies have shown that these studies all give reasonable estimates of the extent of disease in cross-sectional studies (18–20, 22, 24, 26–32). It is in longitudinal studies that there is some disagreement in the literature as to the appropriate method to use.

In longitudinal studies the CT scanner on which the images have been acquired, including both scanner manufacturer as well as the type of scanner used (how many detectors used), and the exposure of the scanner (kVp, mA), are of critical importance. Studies have shown that changing the image reconstruction algorithm can greatly influence the extent of emphysema measured using the threshold cutoff value (33, 34). Furthermore, studies have also shown that changing the X-ray dose of the CT scan can influence the extent of emphysema measured using the threshold approach (35). Therefore, it is important in either cross-sectional studies or longitudinal studies that CT technique is held constant for all parameters, slice thickness, reconstruction algorithm, and X-ray dose. Another group of factors include subject characteristics, including body size and, most importantly, the size of breath that the subject took during the scan. Lung volume CT scanning is an important characteristic to take into account, and there have been methods proposed to try and compensate for this, including spirometrically gating the CT scan or using a mathematical approach to correct for lung volume (18, 32, 36). Spirometrical gating has proven to be problematic and is likely not practical in large multicenter studies; therefore, it has been recommended that a mathematical adjustment of lung volume be applied in all longitudinal studies (18, 19).

AIRWAY ANALYSIS

Airway analysis is the most complex analysis that is in common use today (6, 7, 37–56). Unfortunately, there are almost as many different algorithms in use as there are centers that are use them. New multi-detector CT scanners can now acquire images with near isotropic voxel resolution within a single breath-hold. However, this type of image acquisition requires 0.5-mm slice thickness and, therefore, a CT scanner with a minimum of 64 detectors. While there is and has been much work done on developing the best algorithm to measure airways dimensions, distal airways that are responsible for the airflow limitation in COPD are below the resolution of the CT scanner. Two studies have examined this problem. Using the two-dimensional approach on trans-axial CT scans, Nakano and coworkers (50) showed that the wall thickness in the small airways, measured using histology, was correlated with the wall area in the intermediate sized airways measured with CT. Another study by Hasegawa and colleagues (56) using three-dimensional reconstructions of the airway walls showed that airway wall dimensions in the smallest airways that were measureable (i.e., 6th generation) had the strongest correlation with FEV_1 compared with larger segmental (3rd generation) airways. These data have given investigators hope that airway measurements obtained using CT will provide useful data in the understanding of 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 are no definitive data on the best algorithm to measure the airway wall. While a great deal of research has gone into airway wall algorithms (6, 7, 37, 40, 50, 54–57), 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 definitive data are still lacking in this area. An obvious problem of the three-dimensional approach is that there are now many airways that can be "named," and 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 likely that the size of breath the subject takes will produce very different CT images of the airway tree, thereby affecting all of the data derived from the images. Airway analysis still has a long way to go before it becomes practical in the clinical setting. As such, it remains in the research domain and is limited in its applicability.

X-RAY DOSE

A thorough review of X-ray dose can be found in numerous reviews, including the ones found in the articles in this issue. However, an important feature to bear in mind is that X-ray dose is directly related to the mA setting of the CT scanner (58). While the actual effects of radiation on subjects is still unknown, it is the recommendation that the lowest possible dose be used. The level of radiation dose that can be used is dependent on the age of the subject: the younger the subject, the less the dose that should be used (58, 59). Because image noise within the CT scan is also dependent on the dose of the scan, questions involving the lung parenchyma may be answered using a very low radiation dose while airway analysis may require a higher dose (35, 59).

CONCLUSIONS AND RECOMMENDATIONS

1. Quantitative CT scanning will provide useful data on the lung structure that is responsible for the changes in lung function that define COPD. These structural data are extremely important for understanding both pathogenesis and the effect of therapeutic interventions. As such, it is the recommendation of this workshop that in cross-sectional studies of COPD either the threshold cutoff analysis or the percentile point analysis can be used, as

either provides useful information about the extent of emphysema. For longitudinal studies it was recommended that the volume-corrected percentile approach be used because this approach is less sensitive to minor changes in the technical aspects of the CT scan (image noise caused by CT scanner, reconstruction algorithm, etc.) and more sensitive to changes in lung structure. Volume analysis of the lung has proven to be very robust across many different CT platforms and image analysis algorithms, so the volume measurements are strongly recommended not only for correction of the density data but for studies that require information on lung or lobar volume changes.

2. Airway analysis is extremely interesting, and there are numerous groups actively pursuing this approach. However, this technique is rife with technical and methodological problems that still limit it to the research category, and the workshop was unable to define a statement beyond this point.
3. The CT scanner must be treated just like all measuring devices, and be properly calibrated and used without changing the features of the measuring device. This is especially important for longitudinal studies, in which a simple change in the X-ray dose or the reconstruction algorithm for the images can produce huge changes in the extent of emphysema being measured. Therefore the recommendation of this workshop is that very careful attention be paid to the acquisition of the CT images or none of the other recommendations will be of any use.
4. It is the recommendation of this workshop that the X-ray dose be kept as low as possible in all studies. This workshop was not able to define the definitive X-ray dose setting because that definition depends on the type of study being performed.

In conclusion, CT is a powerful tool for the analysis of COPD. There is much enthusiasm within the CT analysis community that CT can provide very robust and reliable measurements of lung structure. Some of these techniques, such as lung volume and density, are quite mature, but other techniques, such as airway analysis and special feature or "textural" analysis of the lung density, should still be considered in the research phase. However, this should not stop investigators from using these less mature techniques, but should encourage them to continue to develop and refine these techniques so that the anatomy of the lung can be accurately measured. The following articles provide some of the background for the standardization of CT scanning in COPD research in the future.

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. Pare) by GSK for the development of validated methods to measure emphysema and airway disease using CT. He is the co-investigator (with principal investigator D. Sin) on a Canadian Institutes of Health–Industry (Wyeth) partnership grant. There is no financial relationship between any industry and the current study.

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Chair: Harvey Coxson (University of British Columbia)

Co-Chairs: John Newell (National Jewish Health), Stephen Rennard (University of Nebraska), Jan Stolk (Leiden University Medical Center)

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