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Lung parenchyma density and airwall thickness in airway diseases

Aims

To describe the methodology and limitations of non-invasive imaging in quantifying lung structure.

To describe the opportunities for non-invasive imaging in understanding the structure of the lung, and how that relates to phenotyping subjects for clinical trials and longitudinal studies.

The development and proliferation of computed tomography (CT) scanners has greatly increased the information available to clinicians and researchers regarding the airways and lung parenchyma. Current CT scanners provide non-invasive images of these structures *in vivo* similar to those obtained at gross pathological examination. In the 1980s and 1990s these images consisted of thick cross-sectional slices (*i.e.* 10 mm) that appeared “blurry” because of the averaging of structures within the slice. In the last 10 years, the development of multi-detector row CT (MDCT) scanners has allowed the acquisition of sub-mm thickness images of the entire chest within a single breath-hold of 5–15 s. These new images can have the same resolution in the X, Y and Z dimensions (isometric voxels) allowing images to be reconstructed in any orientation without loss of spatial resolution (fig. 1). This has greatly facilitated the

visualisation of airways and vessels that are oriented in a radial pattern around the pulmonary hila. Recent developments in CT have also improved the accuracy of lung density measurements, allowing accurate non-invasive evaluation of the air soft-tissue matrix within the peripheral lung. As a result changes in lung density can be accurately tracked using computer programs. These lung density measurements allow the calculation of the tissue and gas volumes in peripheral lung tissue and correlate with emphysematous lung destruction and hyperinflation of the lung [1–8].

The clinical utility of current CT scanners for non-invasive evaluation of chest disease cannot be overstated. Diseases that present with indistinguishable history and physical findings can be reliably separated on the basis of characteristic alterations in the airway, vascular and lung parenchymal findings on chest CT images. This improves disease

Statement of interest

H.O. Coxson received \$4,800 in the years 2008–2012 for serving on the steering committee for the ECLIPSE project for GSK. In addition, the author was the co-investigator on two multi-centre 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 computed tomography scans in subjects with chronic obstructive pulmonary disease and a service agreement with Spiration Inc. to measure changes in lung volume in subjects with severe emphysema. He has received a fee for speaking at a conference and related travel expenses from AstraZeneca (Australia). He was the recipient of a GSK Clinical Scientist Award in 2010.

HERMES syllabus link:
module D.3.1

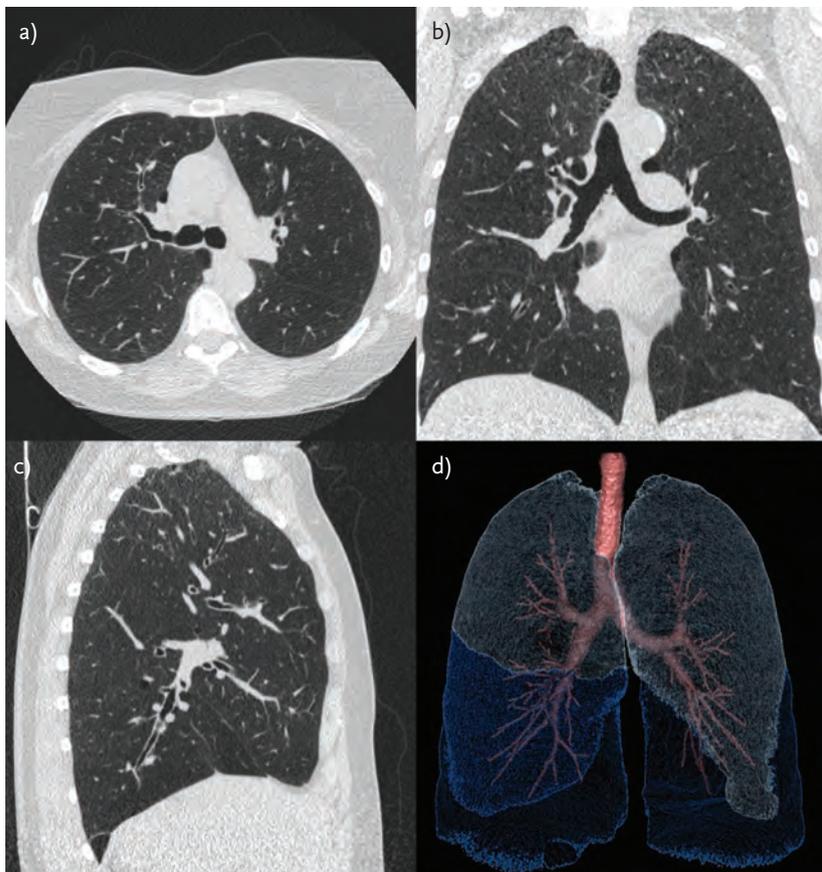


Figure 1

This figure shows a CT scan acquired using a multi-detector row CT scanner. a) The conventional transverse image and the b) coronal and c) sagittal reformats of the CT data are shown. d) A 3-dimensional reconstruction of the airway tree and the lung. (Images were captured using the Pulmonary Workstation 2.0 image analysis software (VIDA Diagnostics, Coralville, IA, USA).

classification, improving the match of disease to treatment. Follow up CT imaging may improve the assessment of treatment, tailoring the selection of drugs and optimising the timing of surgical interventions. Finally, the CT scanner environment is user friendly to patients with respiratory diseases, obtaining diagnostic images using less than a 5-s breath-hold period and presenting a benign environment to monitored and intubated patients.

Quantitative CT analysis of lung parenchyma

It is important to remember that the CT scan images consist of more than the two-dimensional picture elements (pixels) that are displayed on a computer screen (or printed on film). These pixels also contain a third dimension, the thickness of the CT slice, which makes more appropriately titled volume elements (voxels). The fact that these voxels have

a set volume allows an investigator to calculate the volume of the lung by multiplying the number of CT lung voxels by the dimension of the voxel. There is general agreement that most lung segmentation algorithms can reliably and accurately measure lung volume [9]. The recent improvement in these algorithms to accurately measure lobar volume is a direct result of the new MDCT scanners that obtain contiguous thin slice images of the entire lung making it possible to visualise the fissures (fig. 1) [10–16]. Cross sectional studies of lung volume have shown that in COPD there is an increase in lung volume from unaffected levels [2, 17, 18]. Intervention studies using surgical procedures (lung volume reduction surgery) or intrabronchial valves have shown that there is a reduction in either total lung volume (LVRS) [19–23] or the treated lobes (bronchial valves) [24].

The CT scan voxels are also measurements of the apparent X-ray attenuation value of the tissue. This attenuation value, measured in Hounsfield units (HU), gives an indication of the density of the lung and, using this density value, investigators have been able to calculate lung mass, tissue volume and air-space volume [1, 18, 21]. Another derived variable that can be calculated from density is the regional lung inflation, which is an estimate of the volume of gas per gram of lung tissue present in the lung [1, 25]. The extent and severity of emphysema is usually estimated using one of two common methods: the threshold cut-off analysis or the percentile point analysis [1, 2, 5, 6, 22, 26–41]. The threshold analysis, in which the per cent of voxels with attenuation values less than a predetermined threshold point is considered to be emphysema. The most common threshold point in use today is -950 HU [28] even though more recent data suggests that for multi-detector CT scanners -960 HU would be a better cut-off value [42]. It has also been shown that an estimate of the emphysematous lesion size can be performed by plotting the cumulative number of low attenuating voxels (a cluster of low attenuating voxels) that are connected to a neighbouring low attenuation voxel against the cumulative size of this cluster on a log–log plot (fig. 2) [39, 43, 44]. The slope of this relationship is the power-law exponent (D) and subjects with small clusters (emphysematous holes) have a very steep slope (large D) while subjects with large clusters have a very flat slope. This metric has been shown to

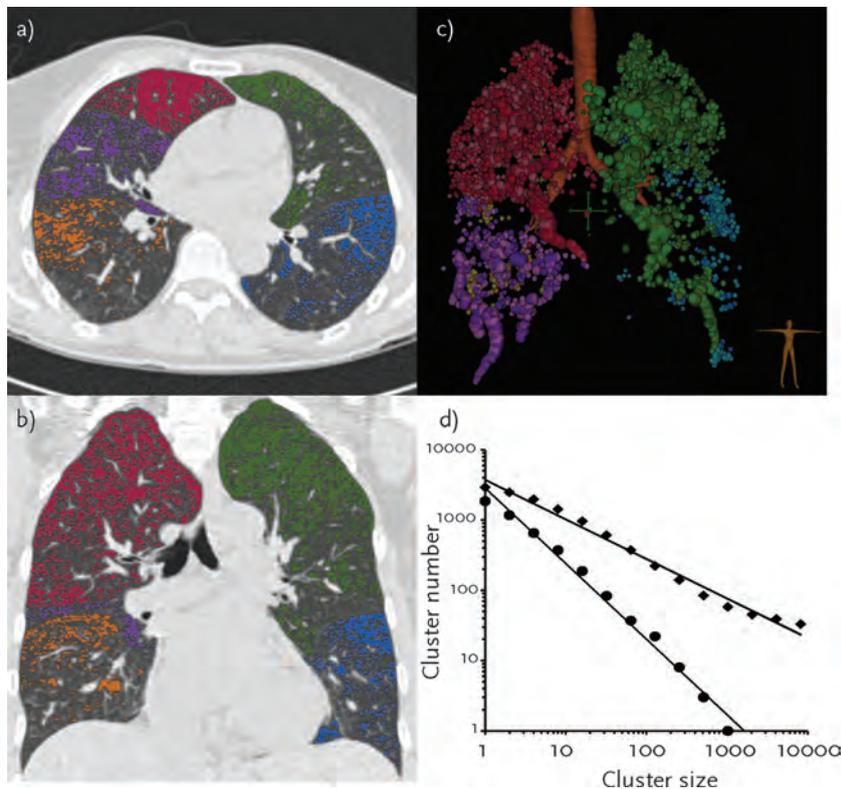


Figure 2

Spatial distribution of low attenuation regions within the lung. The CT voxels with attenuation values less than -950 HU presented in the a) transverse and b) coronal view. Each colour represents voxels from a different lobe. c) Low attenuation voxels are connected to form low attenuation clusters. The number of connected low attenuation voxels is suggestive of larger emphysematous spaces within the lung and are illustrated using low attenuation cluster “balls”. d) A plot of the number of clusters versus the size of the clusters; the slope of this relationship is a power-law relationship (D) and a normal subject with a steep slope (large D) is shown using the circles (\bullet) and a subject with severe emphysema and a less steep slope (small D) is shown using the diamonds (\blacklozenge). Images were captured using the Pulmonary Workstation 2.0 (VIDA Diagnostics, Coralville, IA, USA).

correlate with survival [43] and exercise ability following lung volume reduction surgery [39], but has not been shown to correlate very well with pathological measurements of emphysema [45]. The second approach is the percentile method, in which a specific point on the frequency distribution curve of the X-ray attenuation values is defined and compared between subjects or groups of subjects. The percentile value most commonly used today is the lowest 15th percentile cut-off value [29–37]. Numerous studies have shown that these studies all give reasonable estimates of the extent of disease in cross sectional studies [1, 2, 22, 30–32, 34, 36, 38–41]. It is important to note here that the parameters used to obtain the CT image including the inspiration level of the subject, the slice thickness, the reconstruction algorithm, the exposure of the CT scanner (kVp, mA) and even the type of CT scanner (number of detectors, manufacturer, *etc.*) can all affect these measurements of lung density

[31, 33, 46–49]. A summary of these measurements is shown in table 1.

In a recent workshop hosted by the Alpha-1 Foundation and the COPD Foundation it was recommended that for cross-sectional studies of COPD, either the threshold cut-off analysis or the percentile point analysis can be used as either provides useful information about the extent of emphysema [9]. In 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 [9, 46, 47, 50]. 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.

Table 1. Lung parenchyma and emphysema parameters measured and derived using quantitative computed tomography

Measured parameters		Confounding factors	Derived parameters	
Volume	Sum of voxels	<ul style="list-style-type: none"> • Spatial resolution • Inspiration level 	Mass	Volume X CT density
Total lung	Both lungs or right/left		Tissue volume	Mass/tissue density
Lobar	Sum of voxels on specific lobes		Air volume	Total volume – tissue volume
X-ray attenuation (measured in HU)		<ul style="list-style-type: none"> • Image noise • Inspiration level 	CT density ($\text{g}\cdot\text{mL}^{-1}$)	$(\text{HU} + 1000)/1000$
			Specific lung inflation	$(1/\text{CT density}) - (1/\text{tissue density})$
Low attenuation area	% voxels < pre-defined threshold (<i>i.e.</i> -950 HU)	<ul style="list-style-type: none"> • Image noise • Inspiration level 	Low attenuation Cluster analysis	Slope of regression line of cumulative number of low attenuation clusters <i>versus</i> size of low attenuation cluster
Percentile	HU at pre-defined percentile value of frequency distribution of X-ray attenuation values (<i>i.e.</i> lowest 15th percentile)	<ul style="list-style-type: none"> • Image noise • Inspiration level 		

Table 2. Airway parameters measured and derived using quantitative computed tomography

Measured parameters		Confounding factors	Derived parameters	
Lumen area	A_i	<ul style="list-style-type: none"> • Spatial resolution • Image noise • Inspiration level 	Wall area %	A_{aw}/A_o
Wall area	A_{aw}		Pi_{10}	$\sqrt{A_{aw}}$ at a Pi of 10 mm calculated using regression of measured Pi <i>vs</i> measured $\sqrt{A_{aw}}$
Total airway area	A_o			
Wall thickness	T			
Internal lumen perimeter	P_i			
Branch angle		<ul style="list-style-type: none"> • Contiguous images • Spatial resolution • Image noise 		
Segment length	% voxels < pre-defined threshold (<i>i.e.</i> -950 HU)			

Airway analysis

Recently there has been a great deal of interest in the measurement of airway wall and lumen dimensions (table 2) [11, 12, 51–70]. Originally investigators were limited by the fact that CT scans were cross-sectional images of the lung and therefore measurements of airway dimensions were only performed on airways that were cut in cross section (fig. 3). Studies using these techniques have shown that there is a correlation between airway wall dimensions and airflow limitation (forced expiratory volume (FEV₁)) [62, 67, 70, 71]. However, what everyone recognises is that the airflow limitation in COPD is caused by airways that are below the resolution of the CT scanner. NAKANO *et al.* [64] compared CT measurements and of “medium-to-large” airways to the dimensions of the small airways measured using histology and found that while there was an offset between the two measurements, they were correlated, suggesting that CT measures something in the large airways that reflects the inflammatory changes in the small airways.

The most attractive method for measuring airways today is exploiting the new MDCT scanners to produce three-dimensional reconstructions of the airway tree. This approach has great advantages over the cross sectional approach, because it is now possible to identify and measure a specific airway at a specific location. For example, it is possible to identify the left apical segmental bronchus (LB1) or the right lateral basal segmental bronchus (RB9) and follow it from its origin as far as the reconstruction goes and measure the length of each segment and the angle at branch points (fig. 4) [12]. Using this approach, HASEGAWA *et al.* [70] measured the airway at progressively small generations (*i.e.* 5th or 6th generation) and found that the correlations with spirometry improved in the more distal segments. What these studies have shown is that airway measurements using CT are an important tool in the understanding of COPD but, at the current time, there are almost as many different airway measurement algorithms in use as there are centres that are using them, each with their own strengths and weaknesses. Some of the characteristics of airway techniques are shown in table 2. A more thorough review of these methods can be found in the Alpha-1 Foundation Workshop summary [9, 72]. Finally it should be noted that many of the airways of interest are below the resolution of

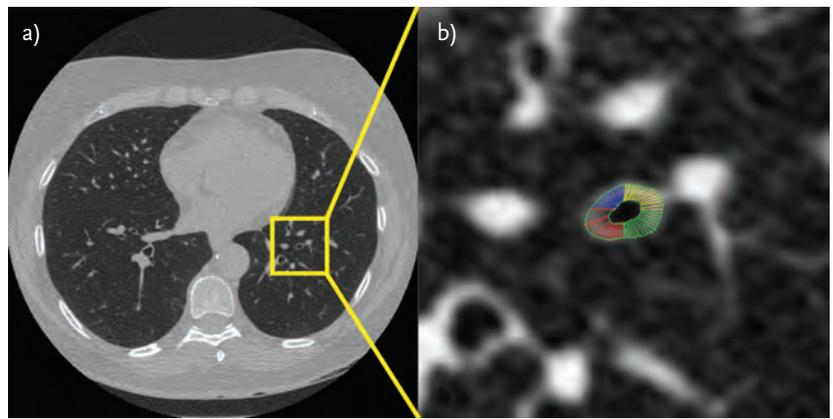


Figure 3

a) Transverse CT image with a region of airways cut in cross section shown in the yellow box. b) Expanded version of the box with a measured airway. Images created using the Emphyxlj image analysis software (University of British Columbia, Vancouver, Canada).

the CT scanner. For this reason investigators have recently turned their attention to expiratory CT scans as a method of measuring the extent of “gas trapping” which is thought to be due to small airway remodelling. To use this technique, investigators obtain CT scans at suspended full expiration. Then, using a threshold value of -856 HU, which has been shown to correlate to maximal lung inflation [1], the percentage of the lung beyond this point is calculated. Since this point can be considered

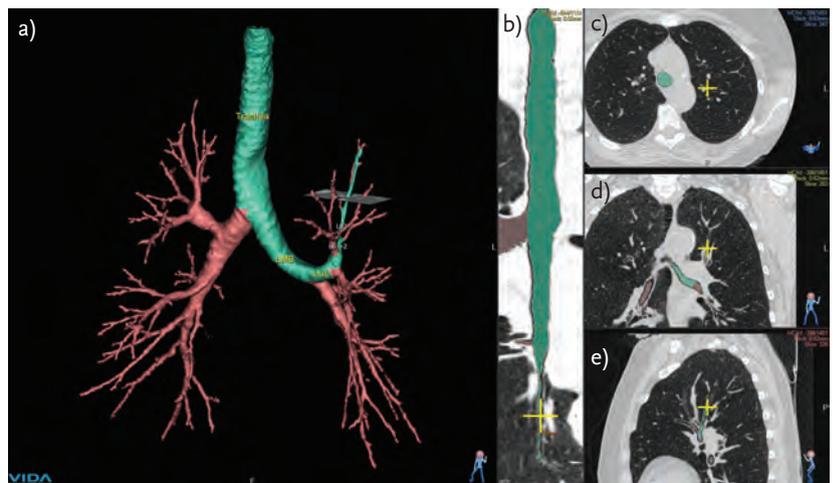


Figure 4

Analysis of the airway tree using a multi-detector row CT scan and commercially available CT analysis software. Using this approach, the airway tree is reconstructed in three dimensions and the airway can be analysed at any location within the tree in a plane that is cross-sectional to the centre line of the airway. a) 3-dimensional reconstruction of the airway tree with the airway path of interest highlighted in green. b) Longitudinal section of a reformatted airway path from a and the yellow cross is the site of the airway measurement and is shown as a small “CT view”. The airway at the site of measurement is shown by the yellow cross in the transverse plane (c), the coronal plane and the sagittal plane (d). (Images created using the Apollo image analysis software (VIDA Diagnostics, Coralville, IA, USA)).

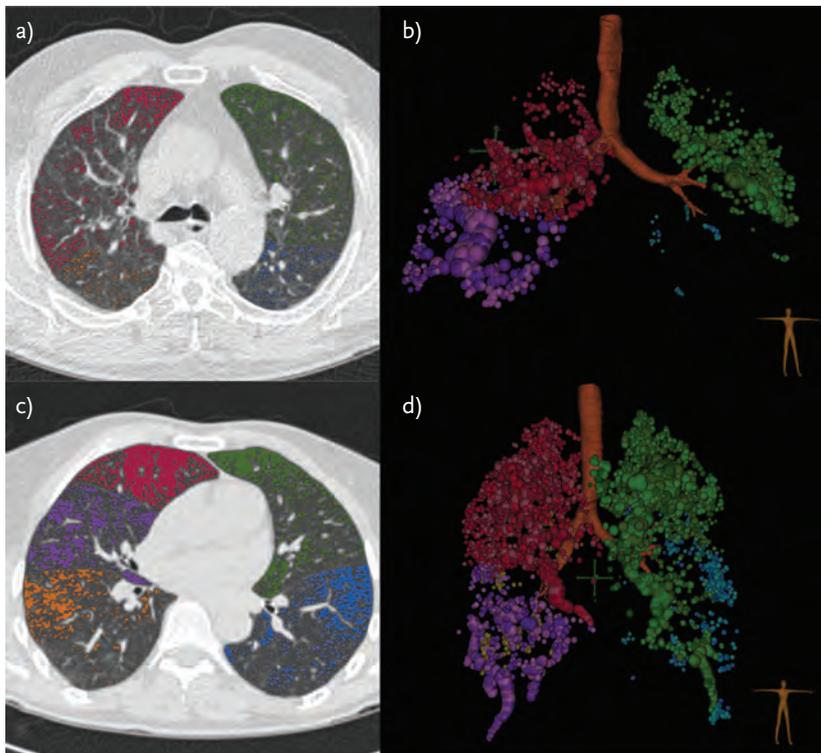


Figure 5

Analysis of the “gas trapping” using expiratory CT scans. The subject in a) and b) exhibits minimal gas trapping as indicated by the lower percentage of voxels below -856 HU (highlighted in colour) while the subject in c) and d) has many more highlighted voxels indicating more severe gas trapping. a) and c) Transverse CT images showing the voxels less than -856 HU; b) and d) show these same voxels using the cluster analysis. Images were captured using the Pulmonary Workstation 2.0 image analysis software (VIDA Diagnostics, Coralville, IA, USA).

maximally inflated, lung with attenuation values less than this point are considered to be hyper inflated and represent gas trapping (fig. 5). While it should be pointed out that this is only a surrogate measurement of airway disease the results have been promising so far. BUSACKER *et al.* [73] have shown in severe asthmatic subjects that those subjects with the most “gas trapping” measured using CT are also the subjects with the most severe asthma symptoms and require the most hospitalisations.

Quantitative studies of COPD using CT

It is well accepted that there are likely numerous phenotypes of COPD. One possible method for understanding the phenotypes of COPD is to understand the anatomy of the lung and this is why CT is so popular in current research protocols. The most obvious place to start when describing the lung structure is to group subjects according to emphysema distribution and airway wall thickness. The distribution of emphysema has shown some

promise in LVRS where subjects with emphysema predominately located in the upper regions of the lung had improved cardiopulmonary exercise ability shortly after surgery and a long-term survival advantage [39, 43, 74]. In one of the first studies to combine measurements of both airway wall dimensions and the extent of emphysema it was shown that both measurements were independently associated with lung function [62]. Furthermore, different aspects of pulmonary function related differently to airways (*i.e.* forced vital capacity (FVC) or emphysema (FEV₁/FVC, diffusing capacity of the lung for CO ($D_{L,CO}$)) and that some subjects could be divided into an airway predominate or emphysema predominate phenotype [62, 71]. Other studies have shown that patients with COPD and the clinical diagnosis of chronic bronchitis had thicker airway walls than those without chronic bronchitis and COPD [75]. This study was followed by another that showed that the distribution of emphysema, centrally (core) *versus* peripherally (rind) and bronchial wall thickness have independent influences on airflow limitation and diffusion of gas [76]. Recently, work by PATEL *et al.* [67] showed that the airway and emphysema phenotypes have a familial association such that COPD patients with increased wall thickness had siblings with increased wall thickness and patients with emphysema had siblings with increased emphysema [67]. It is important to note that none of the published studies so far showed a strong association correlation with lung function but that only further underlines the fact that it is a very complicated task to phenotype individuals with COPD. However, the published data do suggest that measurement of emphysema and airway wall dimensions are important in subjects with COPD because they may give insight into different pathogenic processes responsible for the disease. Finally, there have been several studies that have combined qualitative and quantitative CT measurements of lung structure. One recent study combined qualitative assessment of interstitial lung disease features with quantitative emphysema measurements. This study found that in a COPD cohort changes in lung parenchyma thought to represent interstitial lung disease abnormalities was prevalent (about one out of every 12 HRCT scans) and was associated with reduced total lung capacity and a lesser amount of emphysema [77]. In another study qualitative assessments of emphysema were

combined with quantitative emphysema, and while there was a correlation between the two estimates the best predictor of an increase in qualitative assessment was the quantitative assessment of how the low attenuation areas were clustered together [78].

Limitations to quantitative CT

While CT is a powerful tool for the analysis of lung structure, it does have some limitations and caveats for general use including disagreements on the best method to analyse the lung parenchyma, no definitive study using airway wall algorithms, exposure of subjects to ionizing radiation, and, most importantly, the lack of longitudinal studies involving sufficient numbers of subjects and properly calibrated CT scanners and standardized imaging techniques. It is for these reasons that the Alpha-1 Foundation and the COPD Foundation recently held a workshop on the use of quantitative CT in longitudinal studies where the strengths and weakness of CT were discussed and debated and a full listing of outcome from that meeting can be found in the Proceedings of the American Thoracic Society [9].

X-ray exposure

A discussion of CT is not complete without a comment on its major limitation, a relatively high level of radiation exposure when compared to plain radiography studies (*i.e.* PA and lateral chest radiograph). While the actual effects of the level of radiation exposure delivered in a standard chest CT examination remains controversial there is

increasing evidence that this level of exposure is potentially associated with a small increase in the rate of cancer in long term (>20 years) follow up. It is generally accepted that radiation effects are much more significant in younger compared to older individuals, therefore CT use should be strongly constrained in children, used cautiously in young adults and used prudently in older adults. As well, in all situations it is recommended that the radiation dose be as low as possible for the diagnostic question posed for all CT examinations. This conforms to the time honoured ALARA principle, "as low as reasonably achievable" [79, 80]. Because image noise within the CT scan is also dependant of 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 [49, 80].

Conclusions

In conclusion, it is generally accepted that COPD is a complex disease with complex interactions between genetics and environmental exposures. However, non-invasive imaging such as CT imaging has provided a great deal of hope that with careful anatomic studies correlated with physiologic symptoms this devastating disease can be understood at a level that allows appropriate intervention.

Acknowledgements

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Educational questions

- Which answer best describes the methodology to estimate the emphysema in subjects with COPD?
 - The slope of the relationship between the size of clusters of low attenuating regions within the lung and the number of these regions is thought to represent emphysematous holes
 - The percentage of CT voxels with X-ray attenuation values less than a defined threshold point are considered to be emphysema
 - The X-ray attenuation value at which 15% of the are lower in attenuation is described as emphysema
 - All of the above
- What are some of the major limitations of CT imaging in quantifying of the lung structure: 1) Radiation dose; 2) pathologic validation; 3) appropriate algorithms and method of measurement; 4) lack sufficient longitudinal studies; 5) availability of CT scanners; 6) calibration of the CT scanner?
 - All of the above
 - 1, 2, 3
 - 4, 5, 6
 - 1, 3, 4, 6
 - None of the above

3. There are numerous methods to quantify airway wall structure. Which of these is the most popular method?

- Score guided erosion
- Point spread function
- Full-width-at half maximum
- Model-based algorithms

4. Which of these is an appropriate method to measure gas trapping using CT?

- Threshold analysis at expiration
- Percentile analysis at expiration
- Wall area as a percentage of total airway wall area at expiration
- Lung volume at expiration

5. Non-invasive imaging to understanding the structure of the lung is important because it...

- provides insight into pathogenesis
- can identify response to interventions
- allows the relationship of function to structure
- dose all of the above

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Suggested answers

1. d.
2. d.
3. c.
4. a.
5. d.