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COPD9USA Session Summary

Developing and Implementing Biomarkers and Novel Imaging in COPD

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This article serves as a CME-available enduring material summary of the following COPD9USA presentations:

- "Computed Tomography and COPD" *Presenter*: George R. Washko, MD
- "CT Imaging in Routine Clinical Practice: Are We Ready for Prime Time?" *Presenter*: Meilan K. Han, MD
- "Beyond CT: What MRI can Tell Us about COPD" *Presenter*: R. Graham Barr, MD

Abbreviations: chronic obstructive pulmonary disease, **COPD**; computed tomography, **CT**; magnetic resonance imaging, **MRI**; Hounsfield unit, **HU**; hazards ratio, **HR**; confidence interval, **CI**; pulmonary artery, **PA**; aorta, **A**; ratio of diameter of pulmonary artery to diameter of aorta, **PA/A**; body mass index, **BMI**; Body mass index-airflow Obstruction-Dyspnea-Exercise capacity index, **BODE**; National Lung Screening Trial, **NLST**; Centers for Medicare & Medicaid Services, **CMS**

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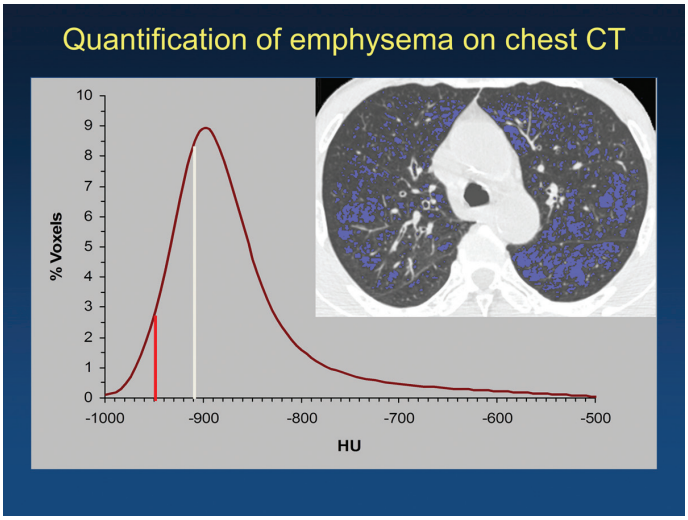
Introduction

Chronic obstructive pulmonary disease (COPD) is defined by airflow obstruction on spirometry and includes emphysema and chronic bronchitis.[1] COPD phenotyping has been heavily influenced by the advent of advanced imaging techniques.[2] While computed tomography (CT) has been used for decades to visualize lung fields, recent advances in quantitative CT imaging have made automated quantitation of emphysema, gas trapping and large airway wall thickness possible.[3] Although the use of magnetic resonance imaging (MRI) for imaging the lung is technically challenging, use of hyperpolarized gases has improved our ability to obtain meaningful information from pulmonary MRI with the added advantage of functional and structural imaging of the heart which may also be affected in COPD.[4] These imaging measures can serve as biomarkers for disease in COPD, and in the future can potentially be used as end points in clinical trials.[5] This is a review of these imaging biomarkers.

Computed Tomography and COPD

CT is increasingly utilized in the diagnosis and characterization of lung disease in COPD.[5] CT has been used for the past 30 years to quantify emphysema.[5] This is done using density mask analyses whereby extrapulmonary tissues are subtracted from the CT images, and all voxels within the lung are assigned a Hounsfield unit (HU) based on their density, and all voxels below a certain threshold are designated emphysematous (Figure 1).[6] This threshold (Eg; -950HU) can then dichotomize the lung into emphysematous and non-emphysematous

Figure 1. Density Histogram for Lung Field with Threshold Selection for Defining Emphysematous Areas



areas and provide a quantitation of percentage of lung affected. Observational studies have shown correlations between quantitative CT measurements of emphysema and airflow obstruction on spirometry, dyspnea measurements, functional capacity and exacerbations.[7-9]

There is an ongoing effort to use CT to phenotype COPD subtypes and also to assess whether we can use CT measurements as intermediate endpoints for clinical studies.[5] For example, Stockley et al showed in an aggregate study of patients with alpha-1 antitrypsin deficiency that using CT can demonstrate differences in loss of lung tissue between patients receiving alpha-1 antitrypsin augmentation therapy and those receiving placebo (annual decline -1.73g/L/yr versus -2.74g/L/yr over 2.5 years of follow-up).[10] CT phenotyping can inform prognosis. Using data from the London COPD cohort, Patel et al showed that COPD patients with bronchiectasis on CT tended to have greater baseline pulmonary inflammation and a prolonged time to recovery from exacerbations.[11] A more recent study showed presence of bronchiectasis on CT is associated with greater risk of death at a median of 4 years (hazard ratio [HR] 2.54; 95% confidence interval [CI] 1.16-5.56; p=0.02).[12] CT can also be used to assess pulmonary vascular disease in COPD. Using CT scans to measure the ratio of the diameter of the pulmonary artery (PA) to the aorta (A), Wells et al found that this ratio (PA/A) independently predicts future exacerbations.[13] The pulmonary vasculature can be visualized on CT and demonstrates distal pruning in COPD, and this correlates with disease severity and a number of measures of respiratory morbidity.[14]

CT can also be used for assessment of extrapulmonary manifestations of COPD. It has long been recognized that spirometry alone does not adequately capture disease severity and manifestations. The Body mass index (BMI)- airflow Obstruction- Dyspnea and Exercise capacity (BODE) index was developed as a composite measure of disease severity, and has been shown to predict mortality.[15] Body tissue composition is perhaps more reflective of disease than BMI. Marquis et al showed that quadriceps cross sectional area measured using CT predicted mortality better than BMI, especially in those with severe COPD.[16]

In summary, CT scans can provide information beyond spirometric assessment alone. It is anticipated that CT scans may be able to serve as intermediate end points in clinical trials by providing assessments of structural lung disease as well as extrapulmonary manifestations which are likely equally important in this complex multisystem disease.

CT Imaging in Routine Clinical Practice: Are We Ready for Prime Time?

Assessment of emphysema on CT images is currently being used for patient selection for lung volume reduction procedures for severe COPD.[17] In this instance, CT emphysema distribution provides information on patient selection that cannot be obtained from spirometric measures of airflow obstruction alone.[18] Some of the newer guidelines, such as from the COPD Foundation, have now incorporated CT emphysema as a disease domain.[19] Other ways that CT may be clinically useful, particularly in early disease is a subject of ongoing investigation.

There is certainly a role for CT imaging in clinical practice, especially for differential diagnosis, prognostication and for treatment planning. The differential diagnosis of dyspnea in a smoker is broad (Figure 2). In some patients, the level of airflow obstruction may be disproportionate to smoking history or may not fit with the clinical profile, in which case CT imaging can provide more information about structural lung disease. Figure 3 illustrates examples

Figure 2. Differential Diagnosis of Dyspnea on CT Imaging

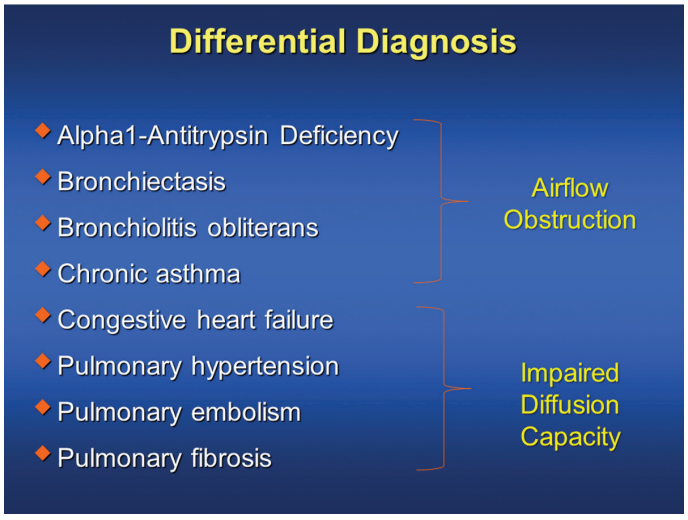
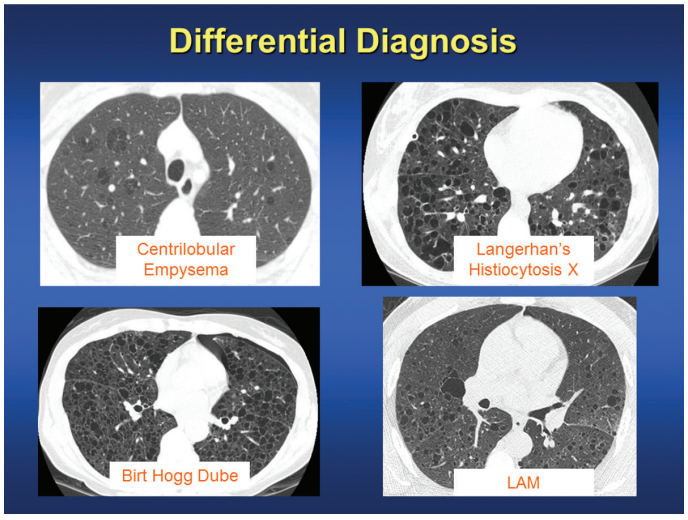


Figure 3. Representative Lung Parenchymal Disease Patterns in Patients with Airflow Obstruction



of patients presenting with airflow obstruction, but with entirely different structural lung diseases, with different prognosis and treatment implications.

While CT is not recommended currently for routine clinical use in all COPD patients, more and more patients will be getting CT scans of the lungs for other reasons. Based on the results from the National Lung Screening Trial (NLST) demonstrating a 20% relative risk reduction in mortality from lung cancer with low dose CT screening, the Centers for Medicare & Medicaid Services (CMS) recently approved CT screening for lung cancer in individuals with at least a 30 pack year smoking history and between the ages of 55 and 77 years and hence at high risk for lung cancer.[20] A significant number of individuals with COPD remain undiagnosed, and it is likely that a substantial number of patients undergoing screening CT scans will show evidence of emphysema and gas trapping.[21] This has important implications for diagnosis and possible interventions such as quitting smoking.

CT can also be used to phenotype COPD beyond the global metric of airflow obstruction, and help predict important outcomes such as exacerbations and mortality.[2] Imaging can help identify pulmonary vascular disease in these patients and this has significant prognostic implications in predicting future exacerbations.[13] The PA/A ratio has been shown to correlate with pulmonary arterial pressures.[22] In some centers, reporting PA/A ratio has become routine in clinical practice. CT imaging is already established for patient selection for lung volume reduction procedures.[17] The National Emphysema Treatment Trial showed that patients with predominant upper lobe disease with low exercise capacity benefit the most from lung volume reduction with both improvements in quality of life as well as mortality.[23] Commercially available software can now provide estimates of emphysema and gas trapping in the clinical setting which will open the doors for clinicians to be able to use quantitative CT imaging data currently being used largely by researchers.

Beyond CT: What MRI Can Tell Us About COPD

While CT imaging is being increasingly used clinically, MRI imaging of the lung is currently used for research and is at a preclinical stage.[4] Compared to CT, the resolution of plain MRI for visualizing lung structure is poor as air is associated with very little signal on MR imaging. Although newer technology has resulted in improvements in image quality, CT is currently better for imaging lung structure.

Alveolar size can be estimated using hyperpolarized gases like Helium-3.[24] These gases display Brownian motion within the alveolar sacs, and this motion can be measured with MRI. With increasing alveolar distension, these metrics can reflect alveolar size and emphysema.[24] As seen in Figure 4 , use of hyperpolarized gases can provide quantitation of emphysema.[25] Early change

Figure 4. Comparison of CT Images (Top Panel) and MRI with Hyperpolarized Helium (Bottom Panel), with Progressive Emphysematous Destruction of the Lung[25]

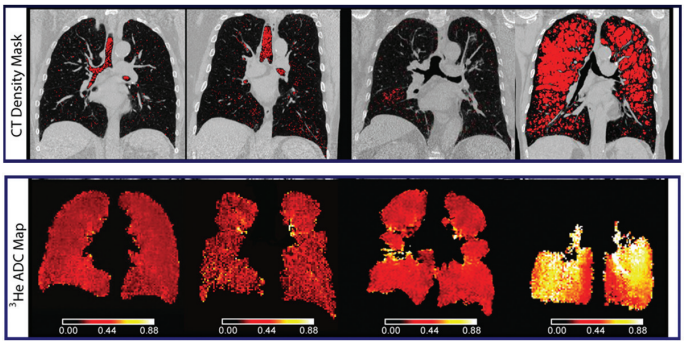
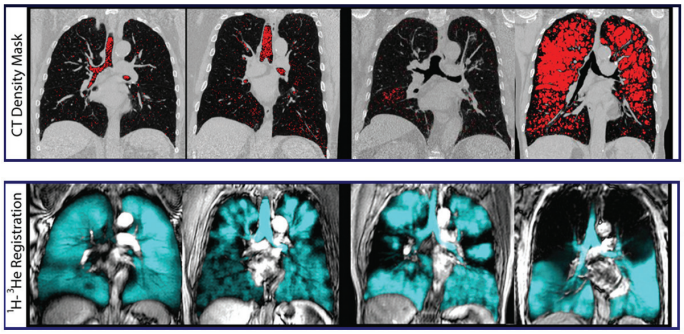


Figure 5. Hyperpolarized Helium MRI Showing Progressively Poor Ventilation with Increasing Emphysematous Destruction of the Lung[25]



Top panel shows CT images and bottom panel shows corresponding MRI images.

and increased alveolar size related to passive smoke exposure have been documented with MR studies in children as young as 5 years old. The resolution permits its use in mouse models as well. Figure 5 demonstrates that with increasing emphysema severity, there are progressively lesser areas of the lung that participate in ventilation, thus providing functional assessments of lung involvement in emphysema.[25] These ventilation defects can also reflect small airways disease. These changes have been shown in asthma patients to be responsive to therapy with bronchial thermoplasty,[26] and since MRI is not associated with radiation risk, MR sequences can be quickly repeated following interventions.

An additional advantage of MRI is that it can provide accurate measures of cardiac structure and function in real time, allowing for assessments of cardiopulmonary interactions, overcoming some of the limitations of echocardiography such as poor windows.[27] For example, multiple studies have shown a relationship between emphysema, lung hyperinflation and decreases in cardiac filling and output.[28-30] Cardiac size and output are affected by lung hyperinflation and this is potentially reversible. At the American Thoracic Society meeting in May 2015, Stone et al showed that using inhaled corticosteroids/long-acting beta agonists decreased air trapping and subsequently improved right and left ventricular filling and cardiac output.[31] This could be an additional mechanism by which these drugs improve symptoms, and this needs further exploration. In addition, the pulmonary microvasculature can be non-invasively assessed using gadolinium contrast[27] A signal intensity map can be created as contrast enters the pulmonary vasculature and special attention can then be focused on the peripheral microvasculature. Even in patients with mild COPD, a loss of pulmonary perfusion can sometimes be appreciated in the peripheral lung fields. Progressively greater loss of pulmonary blood flow is frequently seen with greater degrees of emphysema.

In conclusion, MRI of the lungs can provide images of lung structure similar to CT without the high risk of radiation, with additional advantages of imaging pulmonary microvasculature. Functional MRI can provide estimates of cardiac function and blood flow through the pulmonary microvasculature. These measures can potentially be used as end points for clinical trials, thus shortening the duration of some trials.

Declaration of Interest

Dr. Han has served as a consultant for Boehringer Ingelheim and GlaxoSmithKline. Dr. Washko has served as a consultant for GlaxoSmithKline and his spouse is employed by Merck.

NOTE: To complete the CME post test for this article, refer to the original online version of the article at: ***www.journal.copdfoundation.org***

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