Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Editorial

CT Scanning in COPD – Is it Time to Move On?

Carolyn E. Come, MD[1] George R. Washko, MD[1]

Abbreviations: computed tomographic, **CT**; Hounsfield unit, **HU**; lowest 15th percentile of the density values, **PD15**; Danish Lung Cancer Screening Trial, **DLCST**; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, **ECLIPSE**; forced expiratory volume in 1 second, **FEV_1**; alpha-1 antitrypsin deficiency, **AATD**

Citation: Come CE, Washko GR. Editorial: CT scanning in COPD—Is it time to move on? *J COPD F*. 2015. 2(3): 201-203. doi: http://dx.doi.org/10.15326.jcopdf.2.3.2015.0150

1 Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts

Address correspondence to:

Carolyn E.Come
ccome@partners.org

Keywords:

chronic obstructive pulmonary disease; COPD; computed tomography scanning; CT

The biomedical community is in search of interim study endpoints for the development of novel therapeutics in patients with COPD. Outcomes such as death or spirometric decline require large sample sizes followed for long durations, precluding their use at earlier proof of concept stages of drug development. Imaging is thought to hold promise for both understanding the pathobiology of disease[1] and providing an in-vivo diagnostic that is more sensitive for the detection of disease progression than standard clinical measures.[2] The work published by Thomsen and colleagues in this issue of the Journal[3] provides an opportune segue into a critical examination of recent success amid what have largely become disclaimers about the limitations of longitudinal computed tomographic (CT) scanning.[4]

Several investigations in the mid to late 1980s demonstrated that CT scanning could be used to detect and quantify airspace enlargement in the lungs of smokers.[5,6] By dichotomizing the histogram of lung attenuation values (CT densities) about a Hounsfield Unit (HU) threshold, one could classify lung parenchyma as either pathologic low attenuating tissue, thought to represent emphysema, or higher attenuating, non-emphysematous tissue, with the ratio of low attenuation to total lung tissue representing the percent of emphysematous lung.[6] A second approach to the detection and quantification of pathologic low attenuating lung tissue on CT scan is to identify the HU threshold that demarcates the lowest 15th percentile of the density values (PD15).[7] Numerous previous studies have since demonstrated the clinical correlates of these measures in cross sectional investigation and more recent work has explored their utility in quantifying disease progression.[8]

The CT and functional data aggregated from the Danish Lung Cancer Screening Trial (DLCST)[9] and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)[10] represent information sampled from 2148 participants across multiple international sites. The sheer breadth of data should logically lead to the identification of previously unseen, clinically relevant insights into disease pathophysiology and progression, yet the data did not uniformly support such conjecture. While there was a robust cross sectional association between the PD15 and the forced expiratory volume in 1 second (FEV_1), despite being statistically significant, the change in CT measures of emphysema explained less than 1% of the observed variability in lung function decline. How can this be if densitometric measures of the lung parenchyma accounted for 50% of the observed variability in FEV_1 on correlative investigation?

COPD is characterized as incompletely reversible

expiratory airflow obstruction due to a combination of emphysematous destruction of the lung tissue and obliteration of the small airways. While the relative contributions of these processes to the observed decrements in lung function vary by patient and possibly by time, it is accepted that patients with more emphysema or airway disease generally have lower lung function. Why then doesn't more emphysema on serial CT correlate nicely with declines in lung function over the same period? One possibility is that emphysema does not affect lung function in a linear fashion, i.e., a 5% increase in emphysema does not dependably lead to a predictable decrease in lung function. While longitudinal data is lacking, cross sectional data support this possibility. Critical review of Figure 2 demonstrates that despite the strong correlation between lung function and CT density, there is a high degree of variability in PD15 for any given FEV_1.[3] For example, lung density for study participants with an FEV_1 of 50% predicted ranges from approximately 20 to 120 grams/liter. This may mean that in patients with progressive emphysema on CT, some will have appreciable decrements in lung function and others will have little to no change in FEV_1. Another possibility is that while over a patient's lifetime the progression of emphysema may be linearly-related to decrements in lung function, the 2 may not be tightly correlated at all points in the course of disease (i.e., not evident in limited sampling intervals).

The results of a recent study of augmentation therapy in patients with alpha-1 antitrypsin deficiency (AATD) warrant mention. In a multinational randomized placebo controlled study of 180 patients with AATD, Chapman and colleagues[11] demonstrated that 24 months of intravenous therapy with alpha-1 proteinase inhibitor attenuates the rate of progression of emphysema on CT scan. There was, however, no detectable effect of therapy on FEV_1.

The results of both the augmentation trial and this one by Thomsen and colleagues may reframe our thinking about the use of CT scanning in clinical investigation. While we now more clearly understand the limitations of trying to correlate changes in CT and spirometry over short time periods, we also now find that features of disease on CT scan are dynamic and respond to therapy in a biologically plausible fashion. Maybe the longitudinal data from DLCST and ECLIPSE are proof enough that emphysema progression is associated with decline in lung function and CT is ready to identify promising new therapies in interventional studies.

References

1. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med*;182:598-604. doi: http://dx.doi.org/10.1164/rccm.200912-1843CC
2. Dowson LJ, Guest PJ, Stockley RA. Longitudinal changes in physiological, radiological, and health status measurements in alpha(1)-antitrypsin deficiency and factors associated with decline. *Am J Respir Crit Care Med*. 2001;164 (10 Pt 1):1805-1809. doi: http://dx.doi.org/10.1164/ajrccm.164.10.2106036
3. Thomsen LH, Shaker SB, Direksen A, et al. Correlation between emphysema and lung function in healthy smokers and smokers with COPD. *J COPD F*. 2015. 2(3): 204-213. doi: http://dx.doi.org/10.15326/jcopdf.2.3.2014.0154
4. Vestbo J, Agusti A, Wouters EF, et al. Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. *Am J Respir Crit Care Med*. 2014;189(9):1022-1030. doi: http://dx.doi.org/10.1164/rccm.201311-2006PP
5. Hayhurst MD, MacNee W, Flenley DC, et al. Diagnosis of pulmonary emphysema by computerised tomography. *Lancet*. 1984;2(8398):320-322. doi: http://dx.doi.org/10.1016/S0140-6736(84)92689-8
6. Muller NL, Staples CA, Miller RR, Abboud RT. "Density mask". An objective method to quantitate emphysema using computed tomography. *Chest*. 1988; 94(4):782-787. doi: http://dx.doi.org/10.1378/chest.94.4.782
7. Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med*.1999;160(5 Pt1):1468-1472. doi: http://dx.doi.org/10.1164/ajrccm.160.5.9901055
8. Coxson HO, Dirksen A, Edwards LD, et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. *Lancet Respir Med*. 2013;1(2):129-136. doi: http://dx.doi.org/10.1016/S2213-2600(13)70006-7
9. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. *J Thorac Oncol*. 2009;4(5):608-614. doi: http://dx.doi.org/10.1097/JTO.0b013e3181a0d98f
10. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *Eur Respir J*. 2008;31(4):869-873. doi: http://dx.doi.org/10.1183/09031936.00111707
11. Chapman KR, Burdon JG, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet*. Published online May 2015. doi:http://dx.doi.org/10.1016/S0140-6736(15)60860-1