CHEST

Original Research

COPD

# Not All Measures of Hyperinflation Are Created Equal

## Lung Structure and Clinical Correlates of Gas Trapping and Hyperexpansion in COPD: The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study

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***Background:*** **Hyperinflation refers to a nonspecific increase in absolute lung volumes and has a poor prognosis in COPD. The relative contribution of increased airways resistance and increased parenchymal compliance to hyperinflation of each absolute lung volume is poorly understood. We hypothesized that increased residual volume (RV) and RV/total lung capacity (TLC) would be associated with reduced airway lumen dimensions, whereas increased functional residual capacity (FRC), TLC, and reduced inspiratory capacity (IC)/TLC would be associated with emphysema on CT scan. We examined whether clinical characteristics differed accordingly.**

***Methods:*** **The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited smokers aged 50 to 79 years who were free of clinical cardiovascular disease. Gas trapping was defined as RV or RV/TLC greater than the upper limit of normal and hyperexpansion as FRC or TLC greater than the upper limit of normal or IC/TLC less than the lower limit of normal. Airway lumen diameters and percent emphysema $< -950$ Hounsfield units were quantified on CT images. Analyses were adjusted for age, sex, body size, race/ethnicity, education, and smoking.**

***Results:*** **Among 116 participants completing plethysmography, 15% had gas trapping, 18% has hyperexpansion, and 22% had both. Gas trapping was associated with smaller airway lumen diameters ($P = .001$), greater dyspnea ($P = .01$), and chronic bronchitis ($P = .03$). Hyperexpansion was associated with percent emphysema ($P < .001$), lower BMI ($P = .04$), and higher hemoglobin concentration ($P = .001$).**

***Conclusions:*** **Gas trapping and hyperexpansion on plethysmography were associated with distinct differences in lung structure and clinical characteristics. Absolute lung volumes should not be considered equivalent in their estimation of hyperinflation and provide insight into the extent of airway and parenchymal abnormalities in COPD.** ***CHEST 2014; 145(6):1305–1315***

**Abbreviations:** AWT = airway wall thickness; DLCO/VA = diffusing capacity of lung for carbon monoxide divided by alveolar volume; FRC = functional residual capacity; HU = Hounsfield units; IC = inspiratory capacity; MESA = Multi-Ethnic Study of Atherosclerosis; RV = residual volume; $Spo_2$ = oxygen saturation as measured by pulse oximetry; TLC = total lung capacity

COPD is characterized by airflow limitation that is not fully reversible and is a leading cause of morbidity and mortality.[1,2] Hyperinflation in COPD is defined by an increase in absolute lung volumes[3] and is believed to be partly due to inadequate emptying of the lungs as a result of increases in airways resistance, respiratory system compliance, or a combination of the two.[3] Current guidelines do not specify which absolute lung volumes should be used to define hyperinflation.[4]

Specific lung volumes have been associated with different clinical outcomes in COPD.[5-9] For example, Martinez et al[7] demonstrated increases in residual volume (RV) but not total lung capacity (TLC) to be associated with mortality independent of spirometric measures of airflow limitation. Our group observed increased RV and RV/TLC but not functional residual capacity (FRC), TLC, or inspiratory capacity (IC)/TLC to be associated with greater left ventricular mass independent of body size and traditional cardiac risk

factors.[9] Furthermore, interventions that alter airways resistance (eg, bronchoconstriction, bronchodilation) cause greater changes in RV than FRC or TLC.[5,6,8] In contrast, obesity correlates better with FRC and TLC than RV, and weight loss improves FRC but not RV.[10,11] These studies suggest heterogeneity across absolute lung volumes with respect to hyperinflation, but they did not examine the potential structural basis and clinical correlates of such heterogeneity.

Changes in airway caliber contribute directly to airways resistance,[3,12] and emphysema alters parenchymal recoil in part by lack of elastin.[13] Hence, a differential contribution of quantitative measures of airway dimensions[14] and emphysematous destruction[15] to specific lung volumes, as assessed on CT images, is likely. Some studies have reported simple correlations between specific lung volumes and CT imaging metrics of lung structure[16-19]; however, detailed analyses are lacking.

The aims of the current study were to determine whether elevated RV and RV/TLC are associated with reduced airway lumen dimensions on CT imaging, whereas elevated FRC, TLC, and reduced IC/TLC are associated with emphysema. We then examined whether clinical characteristics differed accordingly.

## Materials and Methods

### *Study Participants*

The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited patients with COPD and control subjects predominantly from MESA, a population-based prospective cohort study of subclinical atherosclerosis,[20] and a separate, nonoverlapping lung cancer screening study.[21] In addition, a small number of participants were recruited from the outpatient community at Columbia University Medical Center. Included participants were aged 50 to 79 years with a ≥ 10 pack-year smoking history. Exclusion criteria were clinical cardiovascular disease, asthma prior to age 45 years, prior lung resection, or cancer. The current report describes participants who were selected for and completed body plethysmography.

### *Study Oversight*

Study procedures were approved by the institutional review board of Columbia University Medical Center (AAAD6395) and by the National Heart, Lung, and Blood Institute. Written informed consent was obtained from all participants.

### *Pulmonary Function Testing*

Body plethysmography, single-breath diffusing capacity of lung for carbon monoxide divided by alveolar volume (DLCO/VA), and postbronchodilator spirometry were assessed with a V6200 Autobox (Sensormedics Corp), Autobox 220 Series instrument (Sensormedics Corp), and a dry-rolling-sealed spirometer (Occupational Marketing, Inc), respectively, following American Thoracic Society/European Respiratory Society recommendations and reported in liters at body temperature and pressure saturated.[22-24] Predicted spirometry values were calculated using reference equations by Hankinson et al.[25] COPD status and severity were defined per American Thoracic Society/European Respiratory Society criteria.[1] Predicted lung volume values and upper and lower limits of normal for each lung volume were calculated using reference equations for participants aged ≥ 65 years by Garcia-Rio et al[26] and reference equations for participants aged < 65 years by Crapo et al.[27]

Gas trapping was defined as RV or RV/TLC above the upper limits of normal. Hyperexpansion was defined as FRC or TLC above the upper limits of normal or IC/TLC below the lower limit of normal.

### *Chest CT Image Acquisition and Analysis*

Participants underwent full-lung thoracic CT imaging on a 64-slice helical scanner (Lightspeed VCT 64; GE Healthcare) (120 kVp, 200 mAs at 0.5 s, 0.75-mm slice thickness). Images were obtained at suspended full inspiration. Image attenuation and airway dimensions were assessed using Apollo software (VIDA Diagnostics, Inc)[28] at a single reading center. Percent emphysema was defined as the percentage of total voxels within the lung field < −950 Hounsfield units (HU).[29]

The airway tree was identified by an automated region-growing technique, and all segmental bronchi were labeled anatomically. Subsegmental bronchi were further labeled along five prespecified paths: RB1, RB4, RB10, LB1+2, and LB10. Luminal diameter and wall thickness were measured perpendicular to the local long axis and averaged along the middle third of each labeled airway. Every scan underwent visual inspection by trained readers unaware of other participant information to confirm accuracy of automated airway labeling.

### *Anthropometry and Other Covariates*

Height, weight, BMI, and blood hemoglobin concentration were measured according to MESA protocol.[11] Age, sex, race/ethnicity, and education were self-reported, and dyspnea was assessed with the five-level (0-4) modified Medical Research Council dyspnea scale.[30] Chronic bronchitis was self-reported and defined by the presence of cough and sputum for at least 3 months in each of

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