Micro-CT analysis of paraffin embedded lung tissue: Is small airway obstruction an early feature of COPD?

Hyun-Kyoung Koo,1,2, Dragos M. Vasilescu,1 Anna E. Scott,1 Jane A. Warner,1 Ian Sinclair,1 Joel D. Cooper,3 James C. Hogg,1 Tillie-Louise Hackett1,2

1Centre of Heart Lung Innovation, University of British Columbia and St. Paul’s Hospital, Vancouver, BC, Canada
2Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada
3Department of Cardiovascular and Thoracic Surgery, University of Pennsylvania, Pennsylvania, USA

ABSTRACT

RATIONALE: Airflow obstruction, the hallmark characteristic of Chronic Obstructive Pulmonary Disease (COPD) has long been attributed to the destruction of small airways and emphysema. However, the relative role of each pathological feature is not well understood. McDonald et al. (NEJM, 2011) recently reported a significant increase in mean airway length and number of small airways in COPD patients compared to controls using computed tomography (CT) scans at clinically relevant lung function. Further, they reported that the loss of terminal bronchioles occurred in regions of lung with normal or mild obstructive airflow obstruction and obstruction of small airways occurred early in COPD and provides the development of emphysema.

METHODS: Lung samples were obtained from patients with known pulmonary function undergoing surgical resection for lung cancer (n = 14; 8 smokers, 6 non-smokers) and formalin-fixed, paraffin-embedded (FFPE). Eight FFPE tissue samples per patient were randomly sampled throughout the lung and extracted using a histological microscope (Bland & Kavanagh) and sections were evaluated to determine mean linear intercept (Lm), number of terminal (T) and respiratory bronchioles (RB) per ml of tissue. Image registration was used to determine the volume of interest and quantitaive analysis was performed using Mucol PKM software for a comprehensive analysis of terminal bronchiole morphology.

RESULTS: Our data demonstrates significant increases in mean airway length and number of small airways in COPD patients compared to controls. When compared to normal lung function controls, COPD patients demonstrated an increase in mean airway length (2.9 ± 0.68 mm) compared to patients with normal lung function (2.1 ± 0.50 mm; P < 0.001). The number of terminal (T) bronchioles (0.7 ± 0.1 per mm) was significantly increased in COPD patients compared to controls (0.3 ± 0.07; P < 0.001) and respiratory bronchioles were also increased in COPD patients (53 ± 10 RB/ml) compared to controls (17 ± 3 RB/ml; P < 0.001). Further, we observed a significant correlation between COPD stage and mean airway length (P < 0.001).

CONCLUSIONS AND CLINICAL SIGNIFICANCE

Micro-CT scans of FFPE lung tissue enables the visualization of small airways. >2mm in terminal diameter and parenchymal structures, not amenable by clinical MDCT.

We demonstrate that there is a decrease in the number of terminal bronchioles in mild to moderate COPD (GOLD I-IV) lungs.

These findings demonstrate that irreversible structural damage in the small distal airways has already occurred despite a preserved FEV1, indicating a need for more sensitive diagnostic tool for early detection.

Our data shows that the obstruction and obliteration of terminal and respiratory bronchioles begins in the presence of small airway emphysema, destruction of airways starts from early stages of disease.

Clinical trials of severe COPD patients have shown that current pharmacological therapies do not slow or reverse the rate of decline in lung function in COPD patients. Our data indicate that earlier therapeutic intervention and lung function assessment may provide a more successful outcome in modulating the progression of this debilitating disorder.

ACKNOWLEDGEMENTS: The authors would like to thank Dr. Orestis Katsumenis, Dr. Mark Elliott, Anriet Samra, Fumago Shaikey and Steven Booth for their excellent technical assistance.