Title: Stereological assessment of parenchyma and small airway morphology using micro-computed tomography in patients with idiopathic pulmonary fibrosis

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Abstract

Rationale: Recent advances in the pathology of idiopathic pulmonary fibrosis (IPF) have indicated that the small airways are involved in the disease process. The aim of this study is to perform a stereological assessment of the microstructure of IPF lungs using micro-computed tomography (microCT) to assess both the three-dimensional morphology of small airways and parenchyma.

Methods: Stereology was used to study explanted air-inflated, frozen lung specimens from patients with severe IPF (n=8) and donor controls (n=8), using a multi-resolution CT imaging cascade. Systematic uniform random (SUR) samples (n=8/lung, 64 total samples in IPF, n=10/lung, 80 total samples in controls) were scanned frozen using microCT to enable assessment of parenchymal morphometry (alveolar surface area, septal wall thickness, and volume fraction of tissue), terminal and transitional (the first order of respiratory) bronchiole number, as well as terminal bronchiolar length and shape, cross-sectional area, wall thickness. Due to the sampling design all values are reported as on a per total lung and on a per sample basis.

Results: Total airway count on specimen CT was increased in IPF cases (561±315) compared to controls (196±113). In IPF lungs, the total number of terminal (1542±562) and transitional bronchioles (2671±928) per lung were drastically reduced compared to controls (terminal 8212±3414, $p<0.001$, transitional 16768±7471, $p<0.001$, respectively). Terminal bronchioles in IPF lungs were significantly thickened ($p<0.001$), dilated ($p<0.001$), and irregular in lumen shape ($p=0.005$) compared to control lungs. In IPF lungs, the alveolar surface area was decreased ($p<0.001$), due to an increase in non-ventilated parenchyma ($p<0.001$) and the remaining functional septal walls were thickened ($p<0.001$) compared to controls. Parenchymal parameters were significantly correlated with all small airway parameters in IPF samples compared to controls. Importantly, terminal bronchiolar wall area and thickness was significantly increased ($p=0.006$, $p<0.001$, respectively) in IPF samples without parenchymal fibrosis, compared to control samples.

Conclusion: Our stereological study confirms that small airway abnormality is a feature of IPF pathology, and correlates with parenchymal remodeling. Furthermore, small airway abnormality may precede

parenchymal fibrosis in IPF, as small airway remodeling is present in regions of the lung without microscopic fibrosis.