Title: Magnetic Resonance Imaging Biomarkers of Airspace Enlargement: Alpha-1 Antitrypsin Deficiency

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Structured Abstract:

Introduction: Alpha-1 Antitrypsin-Deficiency (AATD) is a genetic disorder that results in airspace enlargement leading to early-onset chronic obstructive pulmonary disease (COPD). It remains difficult to monitor lung disease progression in AATD patients using clinical measurements of pulmonary function, such as the forced expiratory volume in 1 second (FEV1) and the diffusing capacity of carbon monoxide (DLCO), as they do not have the sensitivity to detect small changes in lung health [1]. Recently, computed-tomography (CT) measurements of airspace enlargement have proven successful in monitoring disease progression [2], however there are concerns with irradiating patients when serial monitoring is necessary. Therefore, MRI biomarkers are emerging as a potential solution for non-invasive, serial measurements of airway and airspace changes over time [3]. Despite being an attractive alternative to CT, there remain limitations with the current MRI based biomarkers available, due to measurements reflecting only the ventilated lung, causing an artificially low ADC. We hypothesised that a novel 3He MRI biomarker could be developed to overcome these limitations, and be used to sensitively monitor airspace enlargement progression.
Methods: We developed a new biomarker that expresses the ratio of the ADC to the fractional ventilated volume – the ventilatory ADC (vADC). As the VDP increases, the vADC increases, thereby adjusting for artificially low ADC in patients with poor ventilation. Here we evaluated an individual diagnosed with AATD with six visits over 65 months. Pulmonary function tests, the St George's Respiratory Questionnaire (SGRQ), 6-minute-walk-test (6MWT), and hyperpolarized 3He MRI were performed at each visit, while CT was performed during three visits. 3He MRI was used to calculate apparent diffusion coefficients (ADC) – a biomarker of airspace enlargement, as well as ventilation defect percent (VDP) [4], reflecting the fraction of the lung not ventilated during inspiration breath-hold.
Results: In the single AATD patient followed over 65 months there is visual worsening apparent in the 3He ADC and ventilation images. Quantitatively, there were significant annualized changes for FEV1 ($p=0.001$), RA950 ($p=0.02$), vADC ($p=0.02$) and VDP ($p=0.02$), but not DLCO or ADC.
Discussion: We observed that the ADC did not increase significantly, which we hypothesised was due to the lost ventilation, specifically in the basal region of the lung. However, the vADC does significantly increase, indicating it successfully overcomes the previous limitations of ADC. This proof-of-concept study in a single patient presents a novel metric for measuring airspace enlargement, and demonstrates the utility of MRI biomarkers for longitudinal monitoring of AATD.
References: [1] Schluchter, M. et al. Am J Respir Crit Care Med. 2000. [2] Chapman, K. et al. Lancet. 2015. [3] Parraga, G. et al. Invest Radiol. 2007. [4] Kirby, M. et al. Acad Radiol. 2012.