Quantitative Assessment of Idiopathic Pulmonary Fibrosis with Hyperpolarized Gas MRI

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Introduction: Over the past decade, ^{3}He MRI technology has seen rapid development, but the majority of studies have focused on obstructive pulmonary diseases, such as COPD and asthma, rather than interstitial diseases. Idiopathic Pulmonary Fibrosis (IPF), an epitomical interstitial lung disease (ILD), is a debilitating disease with a severe prognosis: The median survival time after diagnosis is 3.2 years. Currently, pathogenesis is unknown and no efficacious treatments have been discovered. Additionally, diagnosis requires biopsies, high resolution CT scans, and global pulmonary function tests (e.g., forced vital capacity or diffusing capacity for CO). ^{3}He MRI is an advantageous diagnostic insofar as it is non-invasive, capable of regional measurements, and affords structural and functional information without exposing the patient to ionizing radiation. Moreover, ^{3}He MRI metrics can provide a convenient means of monitoring the course of IPF in longitudinal animal studies, thus offering a new opportunity for drug development. In this study, the evaluation of apparent diffusion coefficients (ADC) and fractional ventilation with ^{3}He MRI in a bleomycin rat model was shown to be a feasible diagnostic for IPF.

Materials and Methods: 8-week-old male Sprague-Dawley rats between 300 and 350 g were divided into a control group and disease model group. The model rats were given an intratracheal administration of 2.5 U/kg bleomycin, and both groups were imaged after 21 days. The animals were imaged with a 50-cm bore 4.7-T scanner (Varian Inc., Palo Alto, CA) equipped with 12-cm, 25-G/cm gradients and a quadrature 8-leg birdcage body coil (2-3/4" ID). A fast gradient echo imaging pulse sequence was used to obtain a middle coronal slice containing the trachea at a planar resolution of 0.94 mm. Threshold analysis provided a measure of both the mean changes in ventilation and ADC and the intrasubject heterogeneity of these parameters. A percentile threshold is a parameter cut-off value such that an arbitrary percent of bins contain a parameter value larger (for ventilation) or smaller (for ADC) than the threshold. Threshold mapping was employed in two complementary fashions: (1) The threshold parameter value was analyzed as a function of varying percentiles and (2) the percentile was evaluated as a function of varying threshold values. Statistical analyses were performed with custom MATLAB (Mathworks, Natick, MA) programs developed in-house.

Results and Discussion: Histology confirmed that fibrotic progression was as expected: At 3 weeks post-bleomycin, pulmonary response was primarily fibrotic and not inflammatory, and thus representative of IPF. In the threshold analyses, the model group exhibited trends toward decreased ventilation and diffusion coefficients across the lungs, most likely attributable to diminished compliance and alveolar constriction from interstitial inflammation, respectively. This trend was observed in the two types of threshold analysis: variation of ADC and ventilation thresholds and variation of percentile thresholds (see **Figure 1** for an example of percentile threshold at 80% cut-off). **Table 1** contains the results of a two-tailed t-test performed with the group averages of the individual ADC and ventilation means. Ventilation showed a statistically significant difference between the means of the model and control groups. ADC showed an analogous trend, though the means were just under statistically significant difference for a 95% confidence interval.

Conclusion and Future Directions: This preliminary study has corroborated the potential of ^{3}He MRI metrics for assessing pathology in late stage interstitial lung disease in an animal model. Fractional ventilation changes, probably manifestations of reduced compliance, prove particularly promising for the accurate diagnosis of IPF. ADC measurements did not afford the same statistical significance, but did show an analogous trend and may therefore prove helpful if studied within a larger sample. Instructive further investigations with these novel metrics would include testing in human ILD studies and application to ILD animal models in drug studies.

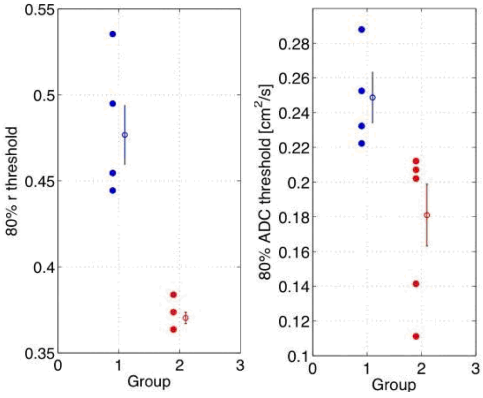

Figure 1. *80% threshold cut-off for fractional ventilation and ADC* (red=mode, blue=control).

	Ventilation		ADC (cm²/s)	
	Control	*IPF*	*Control*	*IPF*
Mean	0.6304	0.5732	0.1908	0.1437
Std. Dev.	0.0383	0.0340	0.0224	0.0367
n	5	6	4	6
P-Value	0.022		0.053	

Table 1. *Two-tailed T-test for ventilation and ADC.*