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Hyperpolarized ^{3}He MRI Ventilatory Apparent Diffusion Coefficient of Alpha-1 Antitrypsin Deficiency

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To the Editor:

Alpha-1 antitrypsin deficiency (AATD) leads to disabling chronic obstructive pulmonary disease (COPD). Current therapy aimed at slowing lung disease progression includes exogenous alpha-1 antitrypsin augmentation therapy, but there are few potential new treatments under development. Currently used measurements of AATD-related emphysema include the forced expiratory volume in 1 second (FEV_1) and the diffusing capacity of carbon monoxide (DL_{CO}); both are relatively insensitive to therapy,[1] although computed tomography (CT) lung density measurements have been shown to worsen more slowly in treated patients.[2]

Hyperpolarized magnetic resonance imaging (MRI) has emerged as a possible alternative or complementary method for evaluating lung microstructure and function.[3] Longitudinal worsening of MRI ventilation-defect-percent (VDP) was shown to be related to symptoms and exercise capacity in COPD patients in whom FEV_1 was not predictive.[4] The apparent diffusion coefficient (ADC) measured using ^{3}He and ^{129}Xe MRI has also been demonstrated in patients with AATD.[5] Although ^{3}He MRI ADC is highly reproducible,[6] these values only report from well-ventilated lung, which is important because as AATD emphysema worsens over time, no inhaled gas MRI information can be gleaned from unventilated lung regions.

Our goal was to develop a new biomarker of AATD emphysema that incorporates functional and microstructural abnormalities that would be sensitive to disease changes over time. We evaluated a single patient with a clinical diagnosis of AATD, who provided written informed consent to study protocols (registered at clinicaltrials.gov as NCT02279329 and NCT02723474), approved by a local Research Ethics Board and federal regulatory agency. He was evaluated using spirometry, plethysmography according to guidelines[7] and MRI at each visit; he also completed the St. George Respiratory Questionnaire (SGRQ), 6-minute walk test (6MWT) and thoracic CT on a 64-slice Lightspeed VCT scanner (General Electric Healthcare, Milwaukee, WI) (64×0.625 mm, 120 kVp, 100 effective mA, tube rotation time = 500 msec, and pitch = 1.0) in breath-hold after inhalation of a 1-L N_2 bag from FRC on visits 2, 4, and 6. The total effective dose was 1.8 mSv (Health Protection Agency of the United Kingdom, NRPB-SR250). MRI was performed on a 3T system (MR750 Discovery, GE HealthCare) as previously described[6] with diffusion-weighted data acquired using a multislice interleaved 2D gradient echo diffusion-weighted sequence for seven 30-mm coronal slices (900 μs selective radio frequency pulse, flip angle $\theta = 4°$, echo time = 3.9 msec, repetition time = 5.6 msec, bandwidth = 62.5 kHz, in-plane resolution = $3.125 \times 3.125\,mm^2$, b = 0, 1.6 s/cm^2); the diffusion-sensitization gradient pulse ramp up-down time = 500 μs and diffusion time = 1460 μs.

The relative area of the CT density-histogram with values < –950 Hounsfield Units (HU) (RA_{950}) and MRI ventilation-defect-percent (VDP) were measured using custom-built (MatLab R2014b; MathWorks, Natick, MA) software.[8] ADC maps were generated using ^{3}He diffusion-weighted images as previously described.[9] To determine regional information, the apical region was segmented from the basal region based on the location of the carina.

It was previously shown in patients with severe COPD that ventilation defects spatially and quantitatively correlated with emphysematous bullae,[10] which reinforces the notion that lung regions with severe emphysema have long time-constants for filling and cannot be ventilated during a short breath-hold scan. To account for this, we considered the diffusing capacity of the lung for carbon monoxide (DL_{CO}) normalized to the ventilated alveolar volume, which generates K_{CO}, as shown in Eq. 1:

$$K_{CO} = \frac{DL_{CO}}{V_A} \quad (1)$$

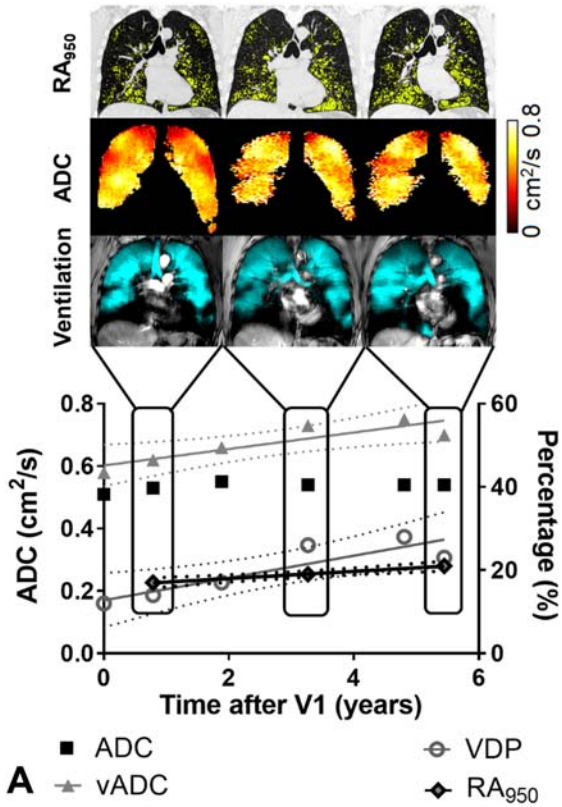
where V_A is the alveolar volume, or the "accessible" volume available for gas exchange. In a similar manner, we proposed to normalize ADC in relation to ventilation, which we term the ventilatory ADC (vADC) as:

$$vADC = \frac{ADC}{1 - \frac{VDP}{100}} \quad (2)$$

We prospectively evaluated a single AATD patient who attended six visits over a 65-month period and received augmentation therapy for the duration of the study, except for a few months between visit 3 and visit 4. At the first visit, where quality of life measurements were recorded, the 6MWD was normal. As shown in Fig. 1A, measurements were evaluated using linear regression with time as the independent variable to calculate slope, r^2, and *P*-value. ^{3}He MRI ventilation and ADC maps show there was qualitative, visually-obvious evidence of increasing ADC values in the apical lung regions and enlarged ventilation defects in the basal lung regions. In Fig. 1A,C, FEV_1 (slope = –1.8, $r^2 = 0.94$, $P = 0.001$), RA_{950} (slope = 0.86, $r^2 = 1$, $P = 0.02$), vADC (slope = 0.03, $r^2 = 0.77$, $P = 0.02$), and VDP (slope = 2.7, $r^2 = 0.79$, $P = 0.02$) significantly changed over time (significant nonzero slope). However, DL_{CO} ($P = 0.70$), ADC ($P = 0.20$), and FEV_1/FVC ($P = 0.05$) did not significantly change. These results, along with other important measures, are reflected in the quantitative results shown in Fig. 1B.

In this proof of concept demonstration, it is important to note that vADC was generated and used based on the assumption that in patients with advanced COPD, ventilation defects are dominated by emphysematous bullae and not airways disease.[10] This is certainly also the case in AATD patients where emphysematous destruction dominates. However, in patients with mild COPD, ventilation defects also derive from gas trapping due to small-

[Correction added on December 20, 2018, after first online publication: The duplication of the author names in the byline was corrected.]



Parameter	V1	V2	V3	V4	V5	V6	*r^2	*p-value
FEV_1 %$_{pred}$	63	64	62	58	55	55	0.94	**0.001**
FEV_1/FVC %	57	56	56	54	54	48	0.65	0.05
DL_{CO} %$_{pred}$	35	55	37	50	50	42	0.05	0.7
6MWD m	N.D	521	N.D	480	480	465	0.85	**0.048**
RA_{950} %	N.D	17	N.D	19	N.D	21	1	**0.02**
ADC cm^2/s	0.51	0.53	0.55	0.54	0.54	0.54	0.37	0.2
Apical ADC cm^2/s	0.45	0.47	0.49	0.51	0.51	0.51	0.89	**0.005**
Basal ADC cm^2/s	0.55	0.57	0.58	0.57	0.57	0.58	0.25	0.3
VDP %	12	14	17	26	28	23	0.79	**0.02**
Apical VDP %	2	2	1	2	4	2	0.2	0.3
Basal VDP %	20	26	28	32	43	32	0.70	**0.04**
vADC cm^2/s	0.58	0.62	0.66	0.73	0.75	0.7	0.77	**0.02**
Apical vADC cm^2/s	0.46	0.48	0.49	0.52	0.53	0.52	0.88	**0.006**
Basal vADC cm^2/s	0.69	0.77	0.81	0.84	1.0	0.85	0.69	**0.04**

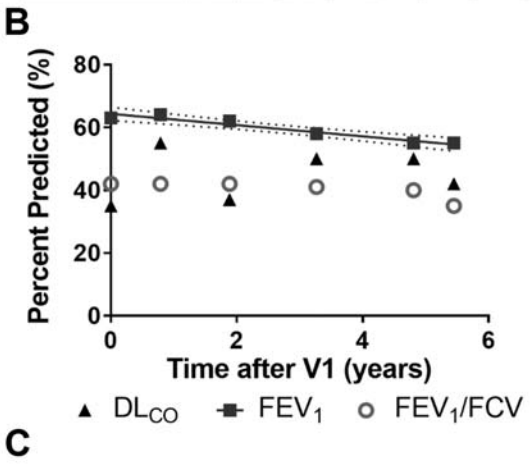


FIGURE1: (A) Longitudinal imaging measurements and ^{3}He MRI static ventilation (cyan) coregistered with ^{1}H MRI; ^{3}He MRI apparent diffusion coefficient (ADC) maps; thoracic CT RA_{950} maps. (B) Participant measurements over 65 months. (C) Clinical pulmonary function measurements, 95% confidence intervals shown for significant regressions. FEV_1 = forced expiratory volume in 1 second; %$_{pred}$ = percent predicted; FVC = forced vital capacity; DL_{CO} = diffusing capacity of the lungs for carbon monoxide; 6MWD = six-minute walk distance; VDP = ventilation defect percent; ADC = apparent diffusion coefficient; RA_{950} = relative area of the CT density histogram of attenuation values < –950 Hounsfield Units; vADC = ventilatory ADC.

airways disease[10] and for these patients, different weightings of the ratio of ADC and VDP should be generated and tested. In this specific AATD patient with GOLD grade 2 COPD and severe emphysema, vADC, and VDP as well as apical ADC, RA_{950}, 6MWD, and FEV_1 significantly changed over the 65-month follow-up period. Somewhat surprisingly, this was not the case for DL_{CO}, perhaps because it can be highly variable over time.

We also observed that vADC significantly increased in both apical and basal regions, whereas VDP did not significantly change in the apical regions and ADC did not significantly change in the basal lung regions. These findings are certainly consistent with previous longitudinal MRI results in COPD patients in whom worsening emphysematous bullae resulted in larger ventilation abnormalities as disease progressed. We acknowledge that vADC has not been widely tested yet and a large-scale study is required in patients with severe emphysema that includes both K_{CO} and patient outcomes. Nevertheless, this preliminary study in a single AATD patient showed that vADC significantly changed while ADC did not. Moreover, vADC changes were concordant with significantly worse 6MWD and CT measurements, which supports its use as a biomarker of airspace enlargement in patients with severe emphysema.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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References

1. Schluchter MD, Stoller JK, Barker AF, et al. Feasibility of a clinical trial of augmentation therapy for alpha(1)-antitrypsin deficiency. The Alpha

1-Antitrypsin Deficiency Registry Study Group. Am J Respir Crit Care Med 2000;161(3 Pt 1):796–801.

2. Chapman KR, Burdon JG, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386:360–368.

3. Kauczor HU, Ebert M, Kreitner KF, et al. Imaging of the lungs using 3He MRI: preliminary clinical experience in 18 patients with and without lung disease. J Magn Reson Imaging 1997;7:538–543.

4. Kirby M, Pike D, Sin DD, et al. COPD: Do imaging measurements of emphysema and airway disease explain symptoms and exercise capacity? Radiology 2015;277:872–880.

5. Ouriadov A, Lessard E, Sheikh K, Parraga G, Canadian Respiratory Research N. Pulmonary MRI morphometry modeling of airspace enlargement in chronic obstructive pulmonary disease and alpha-1 antitrypsin deficiency. Magn Reson Med 2017;79:439–448.

6. Parraga G, Ouriadov A, Evans A, et al. Hyperpolarized 3He ventilation defects and apparent diffusion coefficients in chronic obstructive pulmonary disease: preliminary results at 3.0 Tesla. Invest Radiol 2007;42:384–391.

7. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–338.

8. Kirby M, Heydarian M, Svenningsen S, et al. Hyperpolarized 3He magnetic resonance functional imaging semiautomated segmentation. Acad Radiol 2012;19:141–152.

9. Kirby M, Heydarian M, Wheatley A, McCormack DG, Parraga G. Evaluating bronchodilator effects in chronic obstructive pulmonary disease using diffusion-weighted hyperpolarized helium-3 magnetic resonance imaging. J Appl Physiol (1985) 2012;112:651–657.

10. Kirby M, Pike D, Coxson HO, McCormack DG, Parraga G. Hyperpolarized (3)He ventilation defects used to predict pulmonary exacerbations in mild to moderate chronic obstructive pulmonary disease. Radiology 2014;273:887–896.

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Technical Efficacy: Stage 1