DIFFUSION-WEIGHTED HYPERPOLARIZED HELIUM-3 AND XENON-129 MAGNETIC RESONANCE IMAGING OF ELDERLY NEVER-SMOKERS AND EX-SMOKERS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Target Audience: Scientists and clinicians who are interested in investigating lung disease using hyperpolarized noble gas magnetic resonance imaging (MRI) to non-invasively measure disease morphological and functional changes to gain a better understanding of disease pathophysiology.

Purpose: Hyperpolarized helium-3 (^{3}He) MRI provides a way to regionally quantify lung structure and function in chronic obstructive pulmonary disease (COPD). Unfortunately, the limited access and the high cost of ^{3}He gas has presented serious roadblocks for clinical translation. With recent developments in hyperpolarized xenon-129 (^{129}Xe) polarization technology,[1] ^{129}Xe MRI can now be used to investigate pulmonary disease and provides some distinct differences and advantages compared to ^{3}He MRI. In healthy volunteers and COPD ex-smokers, we previously detected significant and strong correlations between ^{3}He ADC and ^{129}Xe ADC with a b-value of 12s/cm^2, however, it is unclear which b-value associated with ^{129}Xe ADC probes similar spatial scales as ^{3}He ADC. In addition, it is important to determine which b-value associated with ^{129}Xe ADC provides the greatest relationship with standard measures of lung function. In this investigation, our objective was to compare ^{3}He ADC and ^{129}Xe ADC with a b-value of 12s/cm^2, 20s/cm^2 and 30s/cm^2 in the same healthy volunteers and COPD ex-smokers previously evaluated.[2]

Materials

Subjects: All subjects provided written informed consent to a study protocol approved by the local research ethics board and Health Canada. Ex-smokers with a clinical diagnosis of COPD between the ages of 50-85 and a smoking history of ≥10 pack-years were enrolled. Healthy never-smokers were also enrolled who had no history of previous chronic or current respiratory disease. Spirometry and plethysmography were performed and the forced expiratory volume in 1s (FEV_1), functional residual capacity (FRC) and diffusing capacity of carbon monoxide (D_{LCO}) were measured according to the American Thoracic Society guidelines.

Image Acquisition: MRI was performed on a whole body 3.0 Tesla Discovery 750MR (General Electric Health Care, Milwaukee, WI) with broadband imaging capability as previously described[1]. For ^{3}He MRI, a polarizer system (HeliSpin™) was used to polarize ^{3}He gas. For ^{3}He MRI diffusion-weighted imaging, images were obtained using a 2D fast gradient-echo method (FGRE). Two interleaved images (14s total data acquisition, TR/TE/flip angle=7.6 ms/3.7 ms/8°, FOV=40x40cm, matrix 128x128, 7 slices, 30 mm slice thickness), with and without additional diffusion sensitization (G=1.94 G/cm, rise and fall time=0.5 ms, gradient duration =0.46ms, Δ=0.46ms, b=1.6 s/cm^2), were acquired. For ^{129}Xe MRI a commercial turn-key polarizer model XeBox-E10 (Xemed LLC, New Hampshire, USA) was used. For diffusion-weighted imaging, images were obtained using a 2D FGRE. Two interleaved images (16s total data acquisition, TE/TR/flip angle =10 ms/13.5 ms/9°, bandwidth=31.25 kHz, FOV=40x40 cm, matrix 128x80, 7 slices, 30 mm slice thickness, 0 gap), with and without additional diffusion sensitization with a gradient amplitude adjusted to b=12s/cm^2, 20s/cm^2 and 30s/cm^2 (gradient rise and fall time=0.5 ms, gradient separation=2 ms, gradient duration=2.0 ms, diffusion time=5 ms).

Image Analysis: ^{3}He and ^{129}Xe ADC maps were generated using in-house software.

Statistical Analysis: The relationship between ^{3}He and ^{129}Xe ADC and pulmonary function measurements were determined using Pearson correlation coefficients (r) using GraphPad Prism version 4.00.

Results: Table 1 shows subject demographics, pulmonary function measurements and ^{3}He and ^{129}Xe ADC measurements for four healthy never-smokers and four COPD ex-smokers. Figure 1A shows the central coronal ^{3}He and ^{129}Xe MRI ADC maps for a representative COPD ex-smoker. For all subjects, ^{3}He ADC was significantly correlated with ^{129}Xe $ADC_{b=12}$ (r=.98, p<.0001) and ^{129}Xe $ADC_{b=20}$ (r=.91, p=.002) but not ^{129}Xe $ADC_{b=30}$ (r=.60, p=.11) as shown in Figure 1. Table 2 shows Pearson correlations for ^{3}He ADC and ^{129}Xe ADC with pulmonary function measurements. There were significant correlations for ^{3}He ADC with FEV_1 (r=-.72, =0.04), FRC (r=.81, p=.01) and D_{LCO} (r=-1.00, p<.0001); ^{129}Xe $ADC_{b=12}$ was also significantly correlated with FEV_1 (r=-.71, =0.047), FRC (r=.72, p=.046) and D_{LCO} (r=-.98, p<.0001); ^{129}Xe $ADC_{b=20}$ was only significantly correlated with D_{LCO} (r=-.89, p=.003); there were no significant correlations with ^{129}Xe $ADC_{b=30}$.

Discussion: We evaluated ^{3}He ADC and ^{129}Xe ADC with a b-value of 12s/cm^2, 20s/cm^2 and 30s/cm^2 in the same healthy volunteers and COPD ex-smokers previously evaluated,[2] and report that ^{129}Xe $ADC_{b=12}$ and ^{29}Xe $ADC_{b=20}$ were significantly correlated with ^{3}He ADC and with standard measures of pulmonary function. The strong correlations between ^{3}He ADC with ^{129}Xe $ADC_{b=12}$ and $ADC_{b=20}$ suggest that ^{129}Xe diffusion-weighted imaging with b=12s/cm^2 and b=20s/cm^2 is sensitive to lung micro-structural abnormalities and suggests that both methods are probing similar spatial dimensions which is important since the choice of diffusion-weighted gradient can influence the measured ADC.

Conclusions: ^{129}Xe ADC with a b-value of 12s/cm^2 and 20s/cm^2 provides the greatest relationship with ^{3}He ADC and standard measures of lung function.

Table 1. *Subject listing of subject demographic, ^{3}He and ^{129}Xe ADC measurements*

Subject	Age	Sex	FEV_1	D_{LCO}	^{3}He ADC	^{129}Xe $ADC_{b=12}$	^{129}Xe $ADC_{b=20}$	^{129}Xe $ADC_{b=30}$
Never-smokers								
1	49	M	117	95	0.267	0.049	0.043	0.038
2	69	M	101	101	0.233	0.051	0.045	0.033
3	79	F	96	101	0.218	0.050	0.043	0.036
4	69	F	105	94	0.244	0.054	0.041	0.040
COPD Ex-smokers								
1	77	M	34	17	0.626	0.088	0.063	0.039
2	68	F	59	43	0. 514	0.087	0.073	0.057
3	76	M	35	44	0.479	0.080	0.065	0.049
4	71	M	107	42	0.528	0.085	0.071	0.045

Table 2. *Relationships between ^{3}He and ^{129}Xe MRI with pulmonary function measurements*

	Pearson Correlation Coefficients r (p)			
	^{3}He ADC	^{129}Xe $ADC_{b=12}$	^{129}Xe $ADC_{b=20}$	^{129}Xe $ADC_{b=30}$
$FEV_1\%_{pred}$	-0.72 (0.04)	-0.71 (0.047)	-0.60 (0.11)	-0.48 (0.22)
FRC $\%_{pred}$	0.81 (0.01)	0.72 (0.046)	0.57 (0.14)	0.25 (0.55)
$D_{LCO}\%_{pred}$	-1.0 (<0.0001)	-0.98 (<0.0001)	-0.89 (0.003)	-0.60 (0.11)

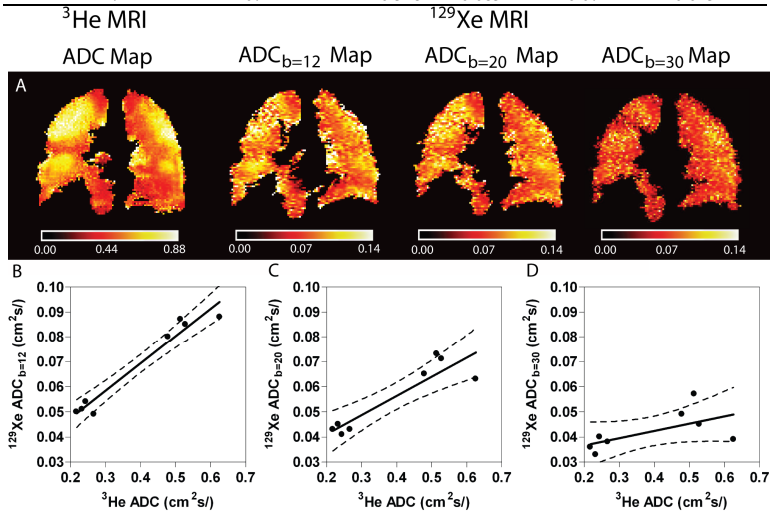

Figure 1. *Correlation between ^{3}He and ^{129}Xe MRI ADC*

A. Central coronal ^{3}He and ^{129}Xe MRI ADC maps.
B. ^{3}He ADC was significantly correlated with ^{129}Xe $ADC_{b=12}$ (r=.98, p<.0001).
C. ^{3}He ADC was significantly correlated with ^{129}Xe $ADC_{b=20}$ (r=.91, p=.002).
D. ^{3}He ADC was not significantly correlated with ^{129}Xe $ADC_{b=30}$ (r=.60, p=.11).

References

(1) Hersman FW, Ruset IC, Ketel S et al. *Acad Radiol* 2008 June;15(6):683-92.
(2) Kirby M, Svenningsen S, Owrangi A et al. *Radiology* 2012 September 5.