Hyperpolarized ^{129}Xe Apparent Diffusion Coefficient Anisotropy in Chronic Obstructive Pulmonary Disease

Alexei V Ouriadov[1], Adam Farag[1], Miranda Kirby[1,2], David G McCormack[3], Grace Parraga[1,4], and Giles E Santyr[1,2]

[1]Imaging Research Laboratories, Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada, London, Ontario, Canada, [2]Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada, London, Ontario, Canada, [3]Division of Respirology, Department of Medicine, The University of Western Ontario, London, Ontario, Canada, London, Ontario, Canada, [4]Department of Medical Imaging, The University of Western Ontario, London, Ontario, Canada, London, Ontario, Canada

Introduction: Hyperpolarized xenon-129 (^{129}Xe) pulmonary magnetic resonance imaging (MRI) is poised for clinical translation mainly due to the stable supply of the gas and the availability of polarizers that provide large volumes of highly polarized gas for MRI studies in respiratory patients (1, 2). In particular, the availability of large volumes (up to 2 L) of highly polarized ^{129}Xe gas provides a way to conduct multiple b value measurements of the ^{129}Xe apparent diffusion coefficient (ADC) in human subjects for the quantitative evaluation of lung tissue microstructure (3). In contrast with the single exponential (ie. two b value) ADC method (3), xenon diffusion anisotropy may be studied with a multiple b value approach (4, 5), yielding transverse (D_T) and longitudinal (D_L) diffusion coefficients. In pre-clinical animal model studies, it has been shown that ^{3}He and ^{129}Xe D_T coefficients are sensitive to lung tissue damage associated with elastase instillation (6, 7). In this pilot study, we explore the potential of ^{129}Xe MRI for the evaluation of diffusion anisotropy changes in a small group of COPD subjects compared to healthy volunteers.

Method: Four healthy volunteers and four COPD ex-smokers provided written informed consent to a study protocol approved by Health Canada and a local ethics board. Imaging was performed at 3.0 T (MR750, GEHC, Waukesha WI) using whole-body gradients (5G/cm maximum) and a custom built, rigid quadrature unshielded asymmetrical RF coil. Two interleaved acquisitions (TE = 9.8 msec, TR = 11.0 msec, matrix size = 128 x 128, number of slices = 7; slice thickness = 30 mm, and FOV = 40 x 40 cm) with and without diffusion sensitization were acquired for a given line of k-space to ensure that RF depolarization (5 degree constant flip angle was used) and T_1 relaxation effects (scan time was 2 seconds per slice) were minimal. The diffusion-sensitization gradient pulse ramp up/down time = 500 μs, constant time = 2 ms and diffusion time = 5 ms; providing four b values: 0, 12.0, 20.0, and 30.0 s/cm^2. The diffusion time of 5 ms was used in order to provide ^{129}Xe ADC sensitivity to alveolar length scales based on simulations (7). For all slices, k space was integrated in the complex domain in pairs then Fourier transformed to obtain a single diffusion weighted and a single non-weighted whole lung projection image for each b value. Hyperpolarized ^{129}Xe (86% enriched, polarization ~15-40%) was provided by a commercial xenon polarizer system (XeBox-E10, Xemed LLC, Durham NH). 1L of a 50/50 hyperpolarized ^{129}Xe/^{4}He gas mixture was inhaled by each subject from functional residual capacity (FRC). For each b value, a single 1L mixed dose was inhaled. All imaging was performed 30 minutes post-salbutamol and after spirometry, plethysmography and diffusing capacity of carbon monoxide (D_{LCO}) measurements were performed.

The following anisotropic diffusion equation (4) was fit to the data using a non-linear least square algorithm (lsqcurvefit.m, Matlab, The Mathworks,Natick MA) to extract $\overline{D}$ (mean diffusion coefficient) and D_{an} (anisotropic diffusion coefficient), D_T and D_L on a pixel-by-pixel basis:

$$S = S_0 \exp(-b\overline{D}) \left(\frac{\pi}{4bD_{an}}\right)^{\frac{1}{2}} \exp\left(\frac{bD_{an}}{3}\right) \Phi\left[(bD_{an})^{\frac{1}{2}}\right] \text{ with } D_L = \overline{D} + \frac{2}{3}D_{an} \text{ and } D_T = \overline{D} - \frac{1}{3}D_{an}$$

where S is the image for each b-value, So is the image for, b=0 s/cm^2 and Φ is the error function.

Statistical Analysis: A multivariate analysis of variance (MANOVA) was performed for statistical comparison of $\overline{D}$, D_{an}, D_T and D_L between the healthy never-smokers and the COPD ex-smokers.

Results: Fig. 1 shows representative maps of mean D_T respectively for a healthy (left) and a COPD (right) subject. Fig. 2 shows the corresponding histograms for these subjects. Table 1 summarizes the pulmonary function measurements, demographic and imaging results for all subjects.

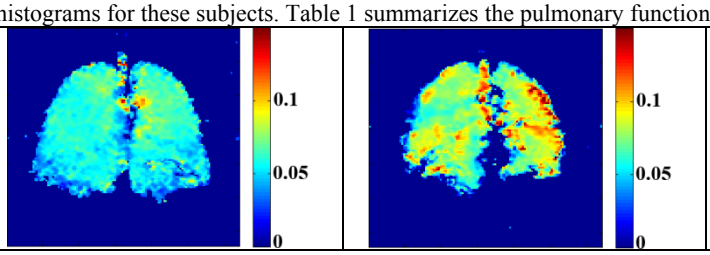

Figure 1. Representative D_T maps for healthy volunteer (left hand side image) and for COPD patients (right hand side image).

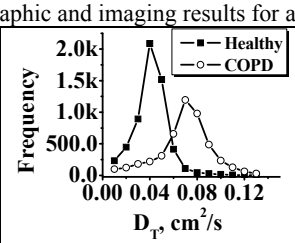

Figure 2. D_T histograms for healthy volunteers and COPD subjects lungs.

Table 1. Study Subject Demographic and Imaging Results.

	Healthy Never-Smokers					COPD Ex-smokers					Significance of
Parameter	S1	S2	S3	S4	Mean (SD)	S1	S2	S3	S4	Mean (SD)	Difference (p)
Age (yrs)	49	69	79	68	66 (13)	77	68	79	71	74 (5)	-
FEV_1 (%$_{pred}$)	96	101	96	105	100 (4)	34	59	35	107	59 (34)	-
FVC (%$_{pred}$)	110	99	95	101	101 (6)	94	86	84	135	100 (24)	-
FEV_1/FVC (%)	69	75	74	79	74 (4)	26	53	31	58	42 (16)	-
D_{LCO} (%$_{pred}$)	121	101	101	94	99 (4)	17	43	44	42	37 (13)	-
$\overline{D}$ 10^{-2} (SD)	5.7 (1.3)	5.8 (1.7)	5.5 (1.5)	5.9 (1.4)	5.7 (1.5)	7.3 (3.3)	8.3 (2.2)	7.5 (2.7)	9.2 (2.9)	8.1 (2.8)	0.002
D_{an} 10^{-2} (SD)	3.7 (1.2)	3.9 (1.8)	3.6 (0.8)	3.6 (1.1)	3.7 (1.3)	3.8 (2.5)	3.0 (1.4)	3.3 (1.5)	2.7 (1.3)	3.2 (1.7)	0.09
D_L 10^{-2} (SD)	8.2 (0.9)	8.4 (1.2)	8.0 (1.2)	8.4 (1.0)	8.3 (1.1)	9.8 (2.3)	10.3 (1.6)	9.7 (2.0)	11.1 (2.2)	10.2 (2.0)	0.001
D_T 10^{-2} (SD)	4.5 (1.5)	4.7 (1.9)	4.3 (1.7)	4.8 (1.6)	4.6 (1.7)	6.6 (3.5)	7.4 (2.4)	6.5 (3.0)	8.4 (3.0)	7.2 (3.0)	0.001

Discussion: We observed significant ^{129}Xe ADC anisotropy differences between healthy age-matched never-smokers and COPD ex-smokers including significantly elevated $\overline{D}$, D_L and D_T and lower D_{an} in COPD. For a single COPD subject with non-obstructive emphysema and no ^{129}Xe ventilation defects (and normal FEV, FEV_1/FVC, abnormal D_{LCO}) we observed the lowest D_{an}, and the highest D_L and D_T. These findings may be useful to test some of the recent hypotheses regarding the earliest pathological events in COPD (8).

References:

[1] Hersman F. W. et al, Acad Radiol; 15, 683–692, 2008.
[2] Cleveland Z. I. et al, J. Phys. Chem. B, 113, 12489–12499, 2009.
[3] Kaushik S. et al, Magn. Res. In Med., 65, 1155–1165, 2011.
[4] Yablonskiy A.et al, Proc. Nat. Acad. Sc., 99, 3111-3116, 2002.
[5] Fichele, S. et al, J. of Magn. Res., 167, 1-11, 2004.
[6] Xu X. et al., MRM 2011. (e-pub ahead of print)
[7] Boudreau M. et al Proceedings of ISMRM 2011.
[8] McDonough J. E, et al, NEJM 365, 1567-1575, 2011.

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