Measurement of ^{129}Xe Gas Apparent Diffusion Coefficient Anisotropy in an Elastase-Instilled Rat Model of Emphysema

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Introduction:

The apparent diffusion coefficient (ADC) of hyperpolarized noble gases (^{3}He, ^{129}Xe) has demonstrated remarkable sensitivity to chronic obstructive pulmonary disease, particularly emphysema [1]. ADC has been demonstrated to behave anisotropically in the lung [2], with the apparent diffusion coefficient consisting of two components: longitudinal (D_L) and transverse (D_T) to the terminal airway. At short diffusion time scales (< 1 ms), D_T of ^{3}He shows significant increases in an elastase-instilled rat model of emphysema [3]. The anisotropic ADC behaviour of ^{129}Xe has not previously been investigated, but may be of significant interest due to the limited availability of ^{3}He gas. However, due to the very small free air diffusion coefficient, it is anticipated that ^{129}Xe will require longer diffusion times (>10 ms) to demonstrate sensitivity to disease and this may be limited by the short T_2* in the lung. Longer diffusion times are possible using lower magnetic field strengths since hyperpolarization is independent of B_0 [4], and T_2* is much longer due to reduced air-tissue susceptibility differences [5]. In this work, we investigate ^{129}Xe gas ADC anisotropy *in vivo* at 74 mT in an elastase-instilled rat model of emphysema. The effect of diffusion time on ^{129}Xe anisotropic ADC measurements is also measured.

Method:

All experiments were performed following a University of Western Ontario Council on Animal Care approved protocol. Healthy Wistar rats were instilled with 70 IU of elastase stock (Elastin Products Company, Owensville, MO) 6-8 weeks prior to imaging for the emphysema disease model, and similar weight-matched rats were instilled with 0.41 ml of saline to serve as controls. Prior to imaging, the animals were anesthetized with a Propofol-Ketamine (10:1) mixture and intubated, tying the trachea tightly around the endotracheal tube for secure breath holds. Ventilation of the animals was performed using a custom ventilator (GEHC, Malmö, Sweden).

Natural abundance ^{129}Xe was hyperpolarized using a custom-built continuous flow ^{129}Xe polarizer. Hyperpolarized ^{129}Xe was extracted from the flowing N_2-He-Xe mixture by freezing it in a custom glass trap in a liquid nitrogen bath placed in a 0.3 T permanent magnet. The Xenon was then thawed into a Tedlar bag, and placed in a reservoir for delivery to the animal with the ventilator. The continuous flow system provided approximately 6 % polarization after the freeze-thaw process. A 74 mT custom-built resistive MR system [6] with maximal gradients of 180 mT/m was used to quantify whole lung diffusion coefficients. Acquisition of the signal was performed with an APOLLO MR console using the accompanying NTNMR software (Tecmag Inc., Texas, USA). A standard Stejskal-Tanner PGSE experiment was performed during 4 second ^{129}Xe breath holds, preceded by four wash-out breaths to minimized residual gases in the lungs [5]. The pulse sequence had the following parameters: the coil was tuned at 0.866 MHz (the Larmor frequency of ^{129}Xe at 74 mT), gradient ramp up/down times of 600 µs and flat times of 800 µs, hard 90° and 180° pulses of 65 µs and 130 µs duration, N=16 was used to acquire both the FID and echo (N=32 total) with dwell times of 100 µs, a 2000 Hz filter and receiver gain of 2000. The gradient strength was varied for 10 b-values ranging from 0 to 99 s/cm^2 in the "x" direction. The experiments were performed for both 6 and 100 ms diffusion times on all rats. This choice of b-values and diffusion times was based on simulations using the budded-cylinder model of Fichele [7, 8] as well as hardware limitations.

Results and Discussion:

Normalized echoes were calculated for each b-value, and the following anisotropic diffusion equation [2] was fit to the data using a non-linear least squares Matlab algorithm (lsqcurvefit.m, The Mathworks, Natick MA) to extract the longitudinal and transverse diffusion coefficients (D_L and D_T):

$$S = S_0 \exp\left[-b\left(D_L + \frac{2}{3}D_T\right)\right]\left[\frac{\pi}{4b(D_L - D_T)}\right]^{1/2} \exp\left[\frac{b(D_L - D_T)}{3}\right]\Phi\left\{[b(D_L - D_T)]^{1/2}\right\}$$

where S is the normalized echo for each b-values, S_0 is the normalized echo for b = 0 s/cm^2 which accounts for T_1 and T_2 and Φ is the error function.

a) Sham-instilled rat **b) Elastase-instilled rat**

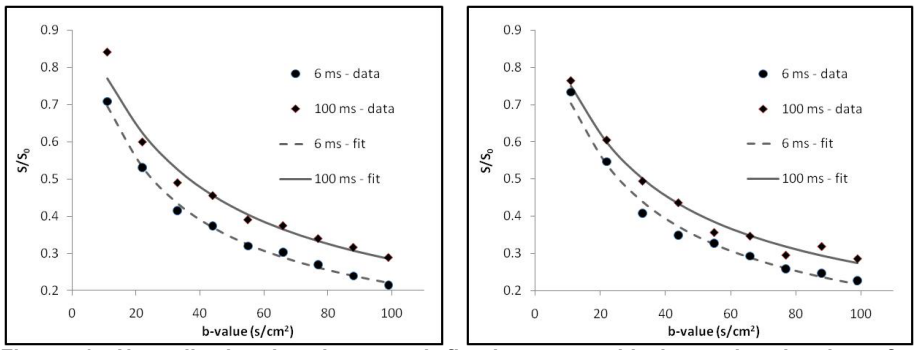

Figure 1. Normalized echo decay and fitted curves with increasing b-values for representative (a) sham-instilled and (b) elastase-instilled rats.

Diffusion Time (ms)	D_L (cm^2/s)		D_T (cm^2/s)	
	Sham	Elastase	Sham	Elastase
6	0.1106 ± 0.0034	0.1052 ± 0.0084	0.0020 ±0.0001	0.0025 ± 0.0003
100	0.0763 ± 0.0115	0.0862 ± 0.0005	0.0013 ± 0.0010	0.0011 ± 0.0005

Table 1. Summary of anisotropic diffusion coefficients at 6 and 100 ms diffusion times for sham and elastase-instilled rats.

Figure 1 shows the echo behaviour with increasing b-value for two representative animals: (a) sham-instilled and (b) elastase-instilled, for both diffusion times. The Yablonskiy model seems to be an appropriate choice for this diffusion time regime, as can be seen from the good fits in Fig. 1. Table 1 summarizes the measured D_L and D_T values at both diffusion times for the rats.

The largest change in D_L was observed at a diffusion time of 100 ms, with a 13% increase for the elastase-instilled compared to the sham-instilled rats. The largest change for D_T was observed at a diffusion time of 6 ms, with a 25% increase for the elastase-instilled rats. It should be noted, that these are whole-lung measurement and it is anticipated that the measured ADC sensitivity may be slightly suppressed by the major airways. We believe that ADC maps obtained by imaging will show even more sensitivity. Overall, measurements of ^{129}Xe gas ADC anisotropy in a rat model of emphysema based on elastase instillation appear to be as sensitive to disease as ^{3}He and thus may offer a viable clinical approach in the future.

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