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 ADC consisting of two components: longitudinal (D_L) and transverse (D_T) to the terminal airway. At short diffusion time scales (< 0.5 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 its very small free air diffusion coefficient, it is anticipated that ^{129}Xe will require longer diffusion times to demonstrate sensitivity to disease. Short T_2^* in the lung at clinical field strengths (>1.0 T) due to air-tissue susceptibility differences may therefore be a limiting factor in investigating ^{129}Xe diffusion with conventional pulse sequence techniques. Longer diffusion times are possible using lower magnetic field strengths due to reduced air-tissue susceptibility differences [4], since hyperpolarization is independent of B_0 [5].

The purpose of this study was to numerically simulate diffusion for a 3-D budded cylinder model of the terminal airways to find the optimal ADC coefficient and diffusion time to detect emphysema using hyperpolarized ^{129}Xe MRI, and then investigate ^{129}Xe gas ADC anisotropy *in vivo* at 73 mT in an elastase-instilled rat model of emphysema.

METHODS

A. Numerical Simulations

A finite difference approach was used to numerically solve the Bloch-Torrey equations [6] in the C programming language for ^{129}Xe diffusion in the budded cylinder model [7] .

Bipolar trapezoidal gradients (Δ=δ) were applied in 30 different orientations relative to the cylinder (0 to π rad) over a range of diffusion times (1 to 100 ms) to simulate random orientation of airways. A phase wrapping boundary technique was used to simulate an infinite cylinder. Geometrical parameters have been previously reported [8].

B. Animal Preparation

This study was approved by the University of Western Ontario Council on Animal Care.

a) Elastase Instillation

Nine male Wistar rats (264 ± 30 g, Charles River Laboratories, Saint-Constant, Canada) were initially anesthetized and were instilled with 75 IU of porcine elastase stock (N=4; Elastin Products Company, Owensville, MO) mixed at a concentration of 175 IU/ml in saline. The remaining rats (N=5) were sham-instilled with 0.43 ml of saline to serve as control [3].

b) Surgical Procedure

Six to eight weeks after instillation, nine male Wistar rats (479 ± 32 g) were anaesthetized and orally intubated for mechanical ventilation by a previously reported technique [9].

C. MR Data Acquisition

A 73 mT custom-built resistive MR system [10] was used to measure whole lung diffusion coefficients. Natural abundance ^{129}Xe was hyperpolarized using a custom-built continuous flow ^{129}Xe polarizer, providing up to 16 to 20 % polarization. The peak inspiratory pressure of the xenon breath holds was kept consistently at 12 cm H_2O by using a flow restrictor and pressured reservoir.

A standard Stejskal-Tanner pulse gradient spin echo whole lung experiment was performed during 4 second ^{129}Xe breath holds, preceded by four wash-out ^{129}Xe breaths to reduce oxygen in the lungs. Eight b-values ranging from 0 to 77 s/cm^2 were performed on each rat for 6, 50 and 100 ms diffusion times. This choice of diffusion times and b-values was based on simulations (see section A above) as well as MR hardware limitations.

D. Data Analysis

D_L and D_T were extracted from the simulated and experimental data by fitting the Yablonskiy anisotropic diffusion model [2] to the numerical and experimental data:

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

where b is the b-value of the pulse sequence, S_0 is the signal for b = 0 s/cm^2, and Φ is the error function. This model was fitted to the data using a nonlinear least squares Matlab algorithm (lsqcurvefit.m, The Mathworks, Natick MA).

Statistical analysis was performed using Prism® (GraphPad Software Inc., California, USA).

RESULTS

A. Numerical Simulations

Figures 2 a) and b) show the simulated dependence of anisotropic diffusion coefficients (D_L and D_T extracted from Eq. 1) on diffusion times for the budded cylinder models of healthy and diseased terminal airways. Figures 2 c) and d) show the difference in these diffusion coefficient between diseased and healthy airways.

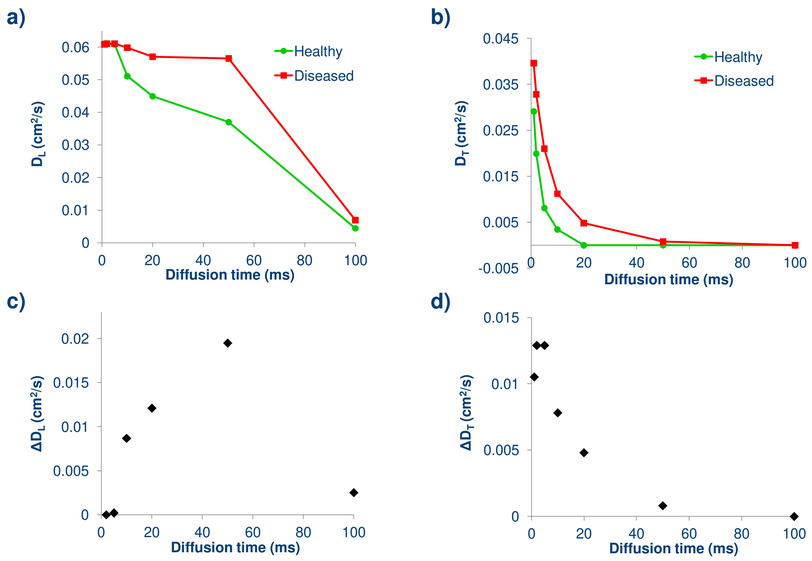

Figure 2. Simulated D_L (a) and D_T (b) as a function of diffusion time for healthy (R_D = 193 µm) and diseased (R_D = 280 µm) terminal airways. The increase in D_L (c) and D_T (d) between normal and diseased lungs are also shown.

B. *In vivo* experiments at 73 mT

The self diffusion coefficient of natural abundance ^{129}Xe was measured *in vitro* to be 0.0559 cm^2/s (r^2=0.9986), which agrees well with the literature values

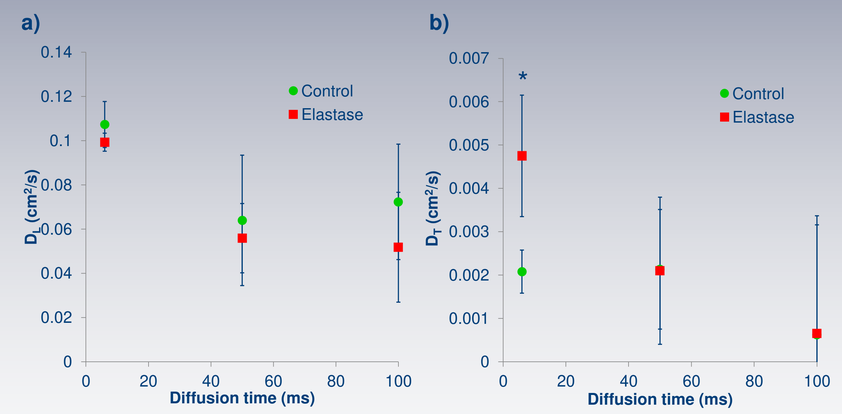

Figure 3. *In vivo* ^{129}Xe longitudinal (a) and transverse (b) diffusion coefficients for three diffusion times (6, 50 and 100 ms) for sham (N=5) and elastase-instilled (N=4) rats.

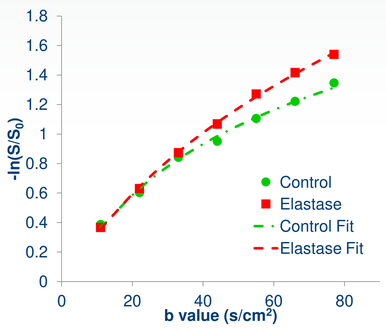

Figure 4. The relationship between –ln(S/S$_0$) and b values (Δ = 6 ms) for a representative sham and elastase-instilled rat.

Figures 3 a) and b) show the measured D_L and D_T for sham and elastase-instilled rats for three diffusion times (6,50 and 100 ms).

Figure 4 shows the relationship between signal (experimental and the fit from Eq. 1) with b values for a representative control and elastase rat for Δ = 6 ms. D_L and D_T extracted from this control sample was 0.1127 and 0.0018 cm^2/s, while for the elastase-instilled sample they were 0.0963 and 0.0060 cm^2/s.

DISCUSSION AND CONCLUSIONS

A significant increase in D_T (128%) was observed between sham and elastase-instilled rats for a 6 ms diffusion time ($p < 0.05$). This agrees well with the range of diffusion times numerically predicted for optimal D_T sensitivity (159% predicted increase for 5 ms, Figure 2 d). No statistically significant differences were observed for D_L and D_T at any other choice of diffusion time. Further investigations are needed to determine if the large variations in measured D_L can be attributed to physiological variations or experimental uncertainties.

Although this study measure 8 b-values to extract ADC components, clinical ADC mapping conventionally uses only two. Figure 4 clearly shows that such a linear approximation may not be appropriate for diffusion times clinically available for ^{129}Xe (<20 ms), and that there are b-values optimally sensitive to emphysematous changes, though the required large gradient strength (>70 mT/m) may not be available on clinical MRI systems.

ACKNOWLEDGEMENTS AND REFERENCES

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