Mapping of ^{129}Xe Apparent Diffusion Coefficient Anisotropy in Radiation-Induced Lung Injury

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Introduction: Magnetic Resonance (MR) imaging of hyperpolarized noble gases (^{3}He and ^{129}Xe) provides anatomical and functional information about the lungs. In particular the ^{129}Xe apparent diffusion coefficient (ADC) can be used to detect alveolar enlargement due to emphysema (1). ADC in the lung is anisotropic and can be described by two components; (i) a longitudinal coefficient (D_L) representing diffusion along the terminal bronchiole and (ii) a transverse coefficient (D_T) representing diffusion perpendicular to the terminal airway (2). ^{3}He D_T has been shown to be particularly sensitive to alveolar damage in a rat model of emphysema involving elastase instillation (3). ^{129}Xe ADC anisotropy may also be useful for early detection of alveolar shrinkage due to radiation induced lung injury (RILI), a significant complication associated with radiotherapy treatment of lung cancer. In this work, ^{129}Xe gas ADC anisotropy was mapped in the lungs of a cohort of rats receiving irradiation and compared to histology.

Method: *All procedures followed animal care protocols approved by the University of Western Ontario (ACVS) and were consistent with procedures used by the Canadian Council on Animal Care (CCAC).* Sprague Dawley rats (~350g) were irradiated with a dose of 18Gy using a ^{60}Co source collimated to expose the right lung only. The rats were imaged two weeks following irradiation. Prior to imaging, the animals were anesthetized, intubated and mechanically ventilated using an MR-compatible ventilator. Breath-hold 2D diffusion-weighted imaging (FOV 5x5cm; Matrix size 64x64; TE 10.3ms; TR 15ms; BW 2kHz, VFA) was performed at 3T (MR-750, GEHC), using a high-performance insertable gradient system, following four breaths of pure hyperpolarized xenon gas (80% enriched in ^{129}Xe) polarized to approximately 10% (XeBox-E10, Xemed LLC, Durham NH). The diffusion-sensitization gradient pulse had a ramp up/down time of 500 μs, constant time of 2000 μs and a diffusion time of 5 ms; providing eight b values ranging from 0 to 115 s/cm^2. The diffusion time of 5 ms was chosen to give best ^{129}Xe ADC sensitivity to alveolar length scales based on simulations (4). Following ADC mapping, the rat lungs were removed, fixed, sectioned and stained for histological analysis.

Results: The anisotropic diffusion equation (3) was fit to the data using a non-linear least square algorithm (lsqcurvefit.m, Matlab, The Mathworks, Natick MA) to extract mean, longitudinal and transverse diffusion coefficients ($\overline{D}$, D_L and D_T), on a pixel-by-pixel basis. Figure 1 shows representative maps of $\overline{D}$ and D_T respectively for a healthy rat (a, b) and an irradiated rat (c, d). Figure 2 shows the corresponding D_T histograms for the whole-lung for these same rats. Table 1 summarizes the whole-lung D_L and D_T results for all rats. Histology confirmed the presence of RILI within both lungs in the irradiated rats.
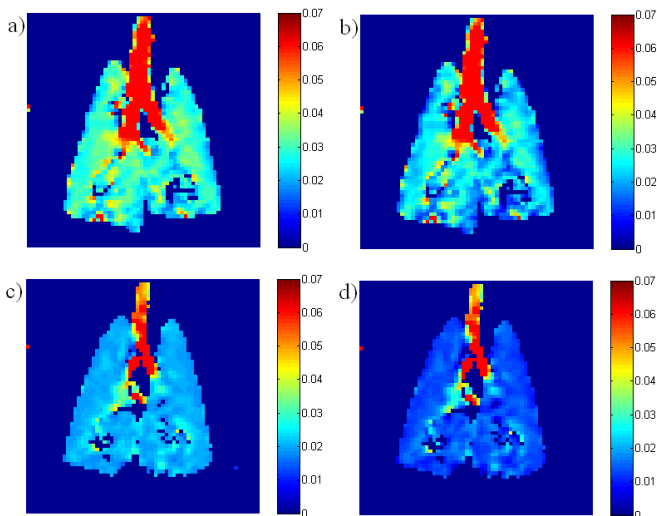

Figure 1. Representative $\overline{D}$ and D_T maps respectively for: healthy rat lungs (a and b) and RILI rat lungs (c and d).
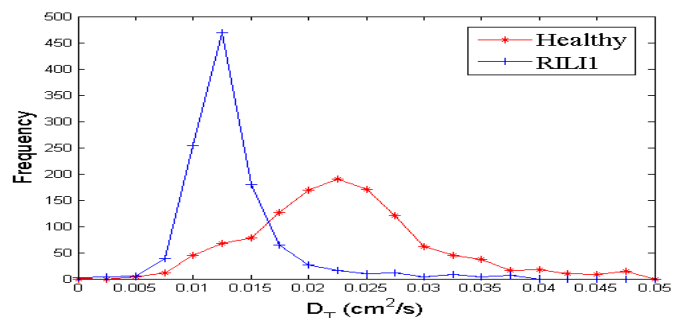

Figure 2. Transverse diffusion coefficient histograms for healthy and RILI whole rat lungs.

	D_T (cm^2/s)	D_L (cm^2/s)
Healthy	0.023±0.006	0.037±0.002
RILI 1	0.015±0.005	0.034±0.001
RILI 2	0.017±0.005	0.027±0.009
RILI 3	0.005±0.007	0.037±0.001

Table 1. Summary of whole lung mean diffusion coefficients for healthy and RILI rats. The values represent the mean D_T and D_L and the error was calculated from the standard deviation of the histograms.

Discussion: Mapping of ^{129}Xe ADC anisotropy resulted in greater discrimination of radiation-induced lung injury compared to mean ADC maps. Specifically, the transverse diffusion coefficient (D_T) was observed to decrease in the irradiated rat cohort as early as two weeks post-irradiation. These changes are consistent with reductions in alveolar radii seen with histology and likely arise from inflammation and/or edema characteristic of the early radiation pneumonitis (RP) stages of RILI. The detection of RILI within both lungs was unexpected. With concurrent developments in clinical hyperpolarized ^{129}Xe imaging, these results are expected to be translatable to human studies in future. Clinically, detection of regional RP may be helpful in order to adjust the radiotherapy fractionation scheme and/or conformation field and/or apply adjuvant therapy to mitigate the effects of RILI.

References:
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