Measurement of Pulmonary Perfusion and Gas Exchange using Hyperpolarized ^{129}Xe in a Rodent Model of Radiation-Induced Lung Injury

OZKAN DOGANAY[1,2], MATTHEW FOX[3], and GILES SANTYR[1,2]

[1]Western University, London, Ontario, Canada, [2]Robarts Research Institute, London, Ontario, Canada, [3]Thunder Bay Regional Research Institute, Ontario, Canada

Introduction:

MR imaging of hyperpolarized (Hp) ^{129}Xe promises to provide unique functional information for diagnosis of lung disease, including ventilation, perfusion and gas exchange. Although most of the inhaled Hp ^{129}Xe stays in gas phase, approximately 2% of Hp ^{129}Xe gas dissolves in the pulmonary tissue and red blood cell (RBC) compartments. The dissolved phases can be spectrally and temporally resolved using a chemically shift saturation recovery (CSSR) pulse sequence, taking advantage of the unique chemical shifts of dissolved ^{129}Xe in the tissue (197 ppm) and RBC (217 ppm) compartments respectively [1]. In CSSR spectra, the transfer time for ^{129}Xe signal from the gas phase to the dissolved phase in tissue, $S_T(t)$, and in red blood cells, $S_B(t)$, carries functional information regarding pulmonary perfusion and diffusing capacity (ie. gas exchange) [2] .Therefore it is anticipated that CSSR will be sensitive to physiological and pathological conditions of lung disease [3]. In this study, we use a theoretical 3-D hyperpolarized gas exchange model to investigate changes in gas exchange and perfusion in a previously published rat model of radiation induced lung injury (RILI) [4].

Methods:

A finite difference approach was used to solve for the CSSR signal dynamics in a simulated geometry consisting of a single alveolus (of 200 ± 5 μm) surrounding by a capillary bed, similar to a previous model [5]. A modification was made to include gas exchange through the alveolar wall thickness. The steps for the modeling were as follows: (i) the velocity distribution of ^{129}Xe, $\mathbf{u_{Xe}}$,within the alveolar sac was calculated from the solution of Navier-Stokes equations, (ii) ^{129}Xe density in the alveolar gas space, $C_G(x,y,z,t)$, was calculated by means of a simple diffusion and convection equations including $\mathbf{u_{Xe}}$ from the first step, (iii) ^{129}Xe uptake in tissue, $C_T(x,y,z,t)$, was estimated by considering the Ostwald solubility constant ($\lambda = 0.2$) in the diffusion equations, (iv) ^{129}Xe uptake in blood, $C_B(x,y,z,t)$, was estimated by again solving the diffusion and convection equations, this time including the blood velocity distribution from the Navier-Stokes equations to address "partial time" effect [3]. Finally, the total amount of ^{129}Xe [mol/m^3] in gas, tissue and blood compartments, $\mathbf{C_G}$ (t), $\mathbf{C_T}$ (t), and $\mathbf{C_B}$ (t), were obtained by integrating over the whole volume of each compartment with a time step of 0.05 s and time duration of 0.5 s (average of 200 for each time step) using Comsol4.2 (Comsol Multiphysics). The initial inhaled concentration of Hp ^{129}Xe at the entrance of the alveolus was approximated to 1.1±0.2 mol/m^3 after 3 breaths of ^{129}Xe. Blood flow and diffusion coefficients were assumed to be 200 ± 10 ml min^{-1} kg and D = 10^{-9} [m^2 s^{-1}] [3].

To validate the model, $\mathbf{C_T}(t)$, and $\mathbf{C_B}(t)$ were compared with $S_T(t)$ and $S_B(t)$ from previously published *in vivo* data set in Ref. [4]. A cross correlation method used to measure similarity between the healthy rat lungs measurements and simulated health data. A normalization factor was obtained by comparing healthy data set and healthy gas exchange model ($N = \mathbf{C_T} / S_T$), from which changes in gas exchange (tissue thickening) and blood perfusion were estimated by fitting the simulated model to previously acquired CSSR experimental RILI data.

Results and Discussion:

Figure 1 (a) and (b) shows experimental CSSR curves from healthy rat lungs (a) and rat lungs two weeks post-irradiation (14 Gy, 1 fraction) (b) respectively. Figure 2 shows simulated $\mathbf{C_T}(t)$, and $\mathbf{C_B}(t)$ curves from healthy rat lungs (a) and rat lungs post-irradiation (b) respectively. As expected, cross correlation of $\mathbf{C_T}(t)$ and $S_T(t)$ curves showed a significant similarities for the healthy ($r=0.88$, $p<0.05$) and diseased model ($r=0.85$, $p<0.05$). Fitting $S(t)_T$ in the simulation model showed an increase in the tissue thickness for the post-irradiated lungs of approximately 50%, consistent with an alveolar wall thickening expected in radiation pneumonitis and confirmed by histology [5]. The simulated post-irradiation model also revealed a drop in the capillary tissue surface of approximately 30% and less blood signal as anticipated due to capillary damage from the irradiation. In future, theoretical analysis of CSSR data from a longitudinal RILI cohort may allow further investigation of RILI mechanisms.

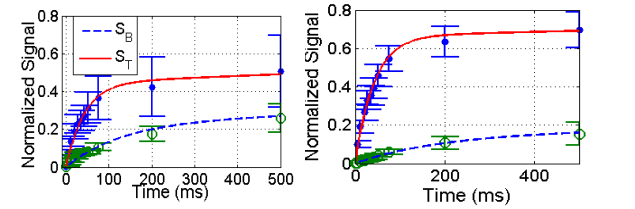

Fig 1. The previously published data set from Ref [4]. Dots represent S_T and S_B data for the average of five rat, and lines represent their exponential fits. (a) Healthy data set; (b) Two-weeks post radiation

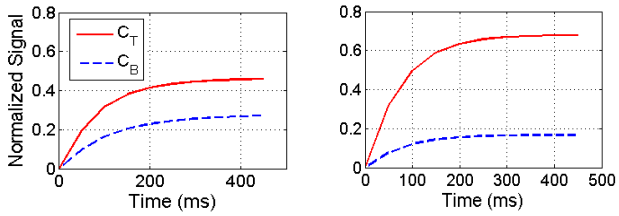

Fig 2. (a) Simulated healthy data set; (b) simulated post radiation data set.

Conclusion:

A theoretical gas exchange model was applied to whole-lung CSSR data from ^{129}Xe dissolved in pulmonary tissue and red blood cells to measure gas exchange and perfusion changes associated with radiation-induced lung injury. The results were consistent with alveolar wall thickening and capillary loss expected in RILI. This model can be used to detect regional changes within the lungs at a stage early enough to modify the radiotherapy plan or administer adjuvant therapy. The model may also be helpful for distinguishing RILI mechanisms (eg. pneumonitis effect from perfusion effects) and could be useful for investigating other forms of lung injury (eg. Ventilator-induced lung injury).

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References: [1] M. S. Freeman et al., MRM 70:1192-1199 (2013); [2] S. Mansson et al., MRM 50:1170-1179 (2003); [3] Y. V. Chang, MRM (note) 000:000-000 (2012); [4] M. Fox, PhD Thesis, Western University, London, ON, (2011); [5] J. Gantelius, The Proc. of the COMSOL Users Conf., Stockholm (2005).