The Role of Collateral Pathways in Long-range ^{3}He Diffusion

J. C. Woods[1], S-E. Bartel[1], S. E. Haywood[2], Y. V. Chang[3], D. A. Yablonskiy[2], D. S. Gierada[2], and M. S. Conradi[1]

[1]Physics, Washington University, St Louis, MO, United States, [2]Radiology, Washington University, St Louis, MO, United States, [3]Children's Hospital of Pennsylvania, Philadelphia, PA, United States

Introduction The long-range diffusion coefficient has been consistently reported at or near 0.02 cm^2/s in healthy human and dog lungs for diffusion distances around 2 cm, both *in-vivo* and *ex-vivo* [1-3]. Previous work has shown the long-range ADC (LRDC, here) to be a sensitive indicator of increased collateral pathways due to emphysema and to correlate well with morphometric changes [4]. There has been little fundamental understanding, however, of the relationship of the measured LRDC to healthy lung structure and the role of collateral pathways, if any, in the healthy lung. In order to determine more precisely this role of collateral routes, we simulated LRDC in a human lung with no collateral pathways, made closed-form calculations of LRDC in a simple lung model, and measured LRDC in several humans, human lungs, and porcine lungs.

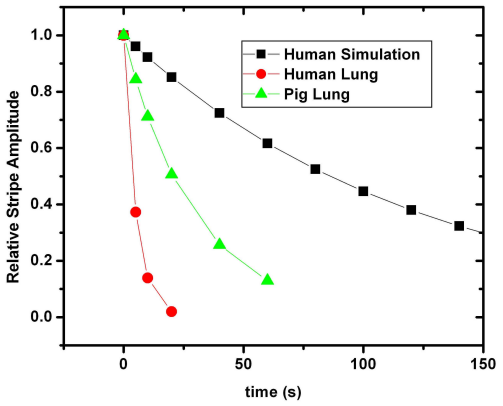
Materials and Methods: The simulations began by generation of a 3-D lung structure as a network of nodes (junctions) in space, with each node singly connected by airways to a parent node and two daughter nodes at 40^o branching angle. The airway radii, lengths, and angles were from published values for the symmetric branching model of human lung [5]. An evolutionary algorithm allowed many different lungs to be "bred" together, to produce lung models with more uniform filling of space. Numerical solutions of the diffusion equation allowed us to follow the magnetization as a function of time and position, after the initial condition of sinusoidal magnetization was imposed. To explore the role of very small amounts of collateral routes, which are known to exist in human lungs, we also modeled diffusion through a number of parallel, semi-permeable barriers with a few, very small holes, via exact calculations using Fick's law of diffusion. The diffusivity was calculated in terms of the number density and size of the pores. Diffusion through alveolar walls, using the Ostwald partition coefficient of ^{3}He in saline, was similarly calculated.

Imaging was performed *in vivo* in 4 healthy volunteers and *ex-vivo* in 5 normal donor lungs (3 donors) that could not be used for transplantation (due to recipient mismatch or other technical reasons) at or near functional residual capacity (FRC) plus 1 Liter of gas. In two cases, LRDC was also measured at lower lung volumes near residual volume, RV. Three explanted porcine lungs were also imaged, since pigs are known to have little or no collateral ventilation [6,7]. All experiments were performed with IRB and/or Animal-Studies approval; *in-vivo* imaging was performed under a ^{3}He IND FDA exemption. We used a single-turn solenoid rf coil with high sensitivity and an 8-channel array for *ex-vivo* and *in-vivo* MR, respectively; both were at 48.47 MHz on a 1.5-T Siemens Magnetom Sonata. After the imposition of sinusoidal magnetization in the head-foot direction, we repeatedly imaged with FLASH; LRDC was calculated by the decay of the first Fourier coefficient at wavelength λ. In-plane resolution was generally 3.5 x 3.5 mm.

Healthy volunteers inhaled a mixture of 0.3 L of hyperpolarized gas and 0.7 L N_2, from approximately FRC. *Ex-vivo* donor and animal lungs were inflated with the ^{3}He/N_2 mixture via gas syringe; imaging was performed at just below TLC (which we defined as 15 cm transpleural H_2O pressure). ^{3}He gas at 40-50% polarization was prepared using spin-exchange optical pumping via a home-built apparatus and a commercial polarizer (G.E.). Each was mixed with N_2 for imaging at the desired inspiration volume.

Results: The simulations revealed that model acini have much shorter time constants (23 s) than the overall decay time constant (110 s) of the modulation pattern, demonstrating that the bottleneck to long-range diffusion at λ = 2 cm resides outside the acini. (This is expected, since acini are efficient at diffusive gas transport by their design and size.) The effective diffusion coefficient at λ = 2 cm was 0.0009 cm^2/s, demonstrating that interacinar diffusion is exceedingly slow by the airways alone (non-collateral paths). This result was consistent across multiple randomly-generated lungs, before and after the evolution algorithm to improve space filling.

Calculations of the diffusion of ^{3}He via Fick's law through alveolar walls, modeled as parallel membranes, revealed an LRDC that was ten times less than the simulations of diffusion via the airways alone, eliminating through-wall diffusion as an important factor. Calculations of the diffusion through parallel membranes with small holes revealed a somewhat surprising result: LRDC = $2nD_0rL$, where n is the number density of the holes and r and L represent the radius of a hole and the wall spacing, respectively. This result implies that a relatively small number of pores can significantly affect the diffusion coefficient; for example, one hole the size of a pore of Kohn (10μ) in the wall of every other alveolus could account for the measured value of 0.02 cm^2/s.



Imaging results are reported in the Table and summarized in the Figure of the decay of the normalized Fourier coefficient. Values for LRDC in human lungs were consistent with our and others' previously reported results [1-4]. Our average LRDC was slightly higher in vivo, however, (0.035 cm^2/s) than our average ex-vivo human (0.019 cm^2/s) result, giving some evidence for the role of cardiogenic mixing and incomplete breath hold in the measurements. There is a clear volume dependence (LRDC increases at increasing volume) and a clear apical-basal dependence, with the average value in the apex higher than the base (average apical increase 35% from the lung's mean). Results from *ex-vivo* porcine lungs demonstrated much lower LRDC than human lungs (average 0.0043 cm^2/s), consistent with the fact that pigs have little to no collateral pathways.

Table	sex	age	wavelength (cm)	LRDC (cm^2/s)	apex (top 1/3)	base (lower 1/3)
Human Ex-Vivo1	F	30	3	0.025	-	-
Human Ex-Vivo2	M	21	2	0.029	0.035	0.027
Human Ex-Vivo3	M	21	2	0.019	0.022	0.017
Human Ex-Vivo4	M	22	2	0.009	0.012	0.007
Human Ex-Vivo5	F	40	3	0.015	0.024	0.011
Human In-Vivo1	M	31	2	0.048	0.074	0.037
Human In-Vivo2	M	26	2.8	0.026	0.031	0.022
Human In-Vivo3	M	23	2.1	0.042	0.047	0.038
low-vol			2.1	0.035	0.040	0.023
Human In-Vivo4	F	25	2.8	0.027	0.058	0.010
low-vol			2.8	0.017	0.048	0.010
Porcine Ex-Vivo1	-	-	2.1	0.0051	-	-
Porcine Ex-Vivo2	-	-	2.1	0.0039	-	-
Porcine Ex-Vivo3	-	-	2.1	0.004	-	-

Conclusions: Our simulations and closed-form calculations indicate that the measured LRDC in humans at $\lambda \geq 2$ cm cannot be due to diffusion through the bifurcating airway tree alone and is extremely sensitive to the extent of collateral pathways. Imaging results in pig and human lungs confirm the role of collateral paths. It is likely that with further modeling, we will be able to quantify the regional extent of collateral pathways in lungs by long-range ^{3}He diffusion.

Acknowledgments

We gratefully acknowledge the National Institutes of Health, via R01 HL 70037 and R01 HL 72369, and to General Electric for use of their ^{3}He polarizer.

References: [1] Owers-Bradley JR, *et al*., *J Magn Reson Imag* 2003; 17: 142. [2] Woods J.C., *et al*., *Magn Reson Med* 2004; 51: 1002 [3] Wang C., *et al. Magn Reson Med 2006; 56: 296.* [4] J.C. Woods, *et al. J Appl Physiol 2005; 99: 1992.* [5] Haefeli-Bleuer B and Weibel ER, *Anat Rec* 1988; 220: 401 [6] Macklem P.T., *Physiol Rev* 1971; 51: 368 [7] Woolcock AJ and Macklem PT, *J Appl Physiol* 1971; 30: 99.