Dependency of Gas Diffusion Measurements in Lung on Respiratory Pressure–Volume

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Introduction: Recent developments in hyperpolarized (HP) gas MRI have turned the measurement of gas apparent diffusion coefficient (ADC) into a strong probe for studying pulmonary airways structure. ADC has shown great promise in detecting changes in lung structure induced by pulmonary diseases, especially in emphysema patients. A great effort is being put toward optimizing measurement techniques and improving the accuracy of measurements regarding the physics of the problem. This includes correcting for gradient imperfections and developing more complex models of signal attenuation in presence of the diffusion-sensitizing gradients. However, perhaps with the exception of a single clinical trial in Malmö University Hospital, the effects of ventilatory parameters on ADC measurements have not been studied systematically. The mechanical behavior of alveoli when exposed to different pressures/volumes is poorly understood. These changes can have substantial effects on the measured ADC values, as they can potentially change the airway volume at the alveolar level. These effects can therefore necessitate a standardization of ventilation protocols associated with ADC measurements, especially when comparing inter– and intrasubject variations, or when performing longitudinal studies. In this work we present for the first time the results of a systematic study tidal volume (TV) effect (or the corresponding PIP) on ADC values measured in a rat lung, along the three primary directions. Experimental results are compared to a well-developed lung model including small airways and alveoli.

Methods: For the experimental measurement of helium diffusivity in the lung, a rat was intubated and connected to a custom-designed small animal ventilator (SAV). Our SAV is capable of delivering the breathing gas at each breath with an accuracy of ±100μL. A pressure sensor attached to the tracheal tube monitors real-time PIP. The rat was maintained on normal air at 80 breaths per minute (BPM) with I:E=1:2 at TV=3.4mL. For HP ^{3}He MRI, the animal was hyperventilated with single large breath of helium at TV=5mL (equivalent to PIP=17cm-H_2O), followed by two helium breaths at the desired tidal volume (Figure 1). Breath was held at end inhalation of the third helium breaths, during which diffusion-weighted gradient echo images were acquired using a bipolar-gradient with the diffusion time Δ=1.5ms, and *b*-values = 0, 5.27, 3.09, 1.41, and 0 sec/cm^2. Other imaging parameters include: FOV=6cm, ST=10mm, RES=64×64 and flip angle=5°. ADC was measured along the three primary Cartesian directions, corresponding to readout (RO), phase encode (PE) and slice select (SL). The TVs used for this study are shown in Table 1, along with their respective inhale times (T_i) and PIPs. To gain insight into the expected ADC changes during lung inflation, we made use of a recently developed computational model of the acinar airways [1]. Because the inhaled gas is predominantly contained within the acinus, we did not extend the simulation to larger airways. Briefly, the acinar unit is represented as a connected tree of space-filling truncated octahedrons, in which connecting faces are removed to ventilate the entire volume while maximizing surface area and minimizing path length to each alveolus. This model has been shown to replicate several important features of histological studies.

Acquisition		a	b	c	d	e	f	g	h
T_i	[sec]	0.6	1.0	1.25	1.5	2.0	2.5	3.0	3.5
PIP	[cm-H_2O]	2	4	8	9	10	12	15	17
TV	[mL]	0.6	1.0	1.8	1.9	2.0	3.0	4.2	5.0

Table 1. Summary of the range of tidal volume and corresponding tracheal pressure and inhale time used for ventilating the rat during ADC measurements

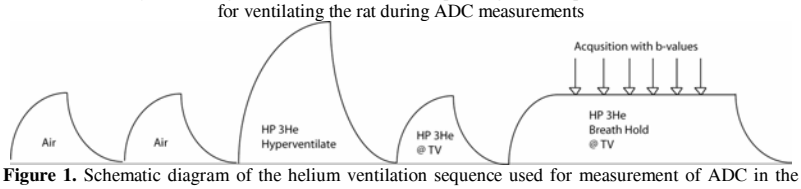

Figure 1. Schematic diagram of the helium ventilation sequence used for measurement of ADC in the lung of the rat.

Results and Discussion: Figure 2 shows representative images from this study depicting with increasing TVs. Mean ADC values for each of the given TVs are plotted in Figure 3. The trachea and bronchi are manually excluded from this analysis since their contribution is close to free diffusion and do not demonstrate the same elastic properties as that of the lung parenchyma. Also shown are linear fits to each of the three directions. It can be seen that the gas diffusivity is more or less isotropic in the imaged slice regardless of the inhaled volume. Additionally, the ADC value increases monotonically with the inhaled volume. It is important to note that ADC values do not change at the same rate over the entire range of tidal volume. More rapid changes in ADC values are observed in the lower volume range as opposed to the higher values. These findings suggest a potential difference in expansion rates of small airways and alveoli subject to a given pressure and may indicate that certain ranges of inhaled volumes can provide better robustness in ADC measurements. Because of the complex topology of the acinar unit, and the uncertainty about the dynamics of airspace expansion during inflation, it is difficult to predict ADC values or scaling with lung expansion. Because of its dominance in lung airspace, the expansion of the acinus must approximate the overall lung expansion, but whether this is predominantly accounted for by small airways or alveolar space is unknown. For comparison to the experimental data, we have assumed that the entire acinus expands together, and find that the predicted ADC is well represented by a linear dependence on overall acinar length scale (or a 1/3 power law dependence on volume). This experimental data shows a significantly faster dependence. In addition, the measured ADC values are larger by approximately a factor of two (at FRC; TV=0) to three (at end inspiration) than would be predicted. The lower curve in Figure 3 shows the predicted ADC based on the above model and scaling, and a free diffusion coefficient of 2.05 cm^2/s. We note that although the gas inside the lung is not pure ^{3}He, the simulated dependence on free diffusion coefficient is relatively weak, and therefore postulate that topological changes during inflation may be primarily responsible for this difference.

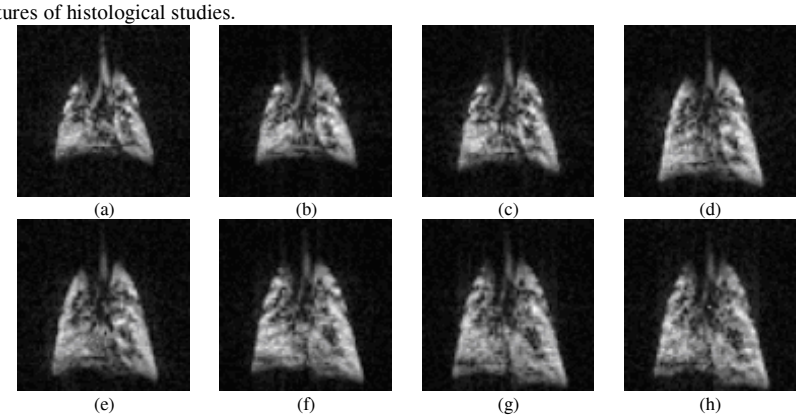

Figure 2. Representative images of the rat lung subjected to an increasing sequence of tidal volumes.

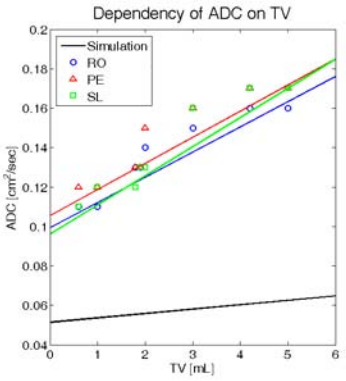

Figure 3. Variation of ADC along the three primary axes as function of tidal volume.

Conclusion: Preliminary results indicate that ADC measurements in the lung are strongly dependant on the inhaled volume of HP helium. This dependency is stronger in the lower ranges of tidal volume, i.e. within the range of natural tidal volume. It is necessary to extend this study to a large number of subjects in order to establish statistically significance of the observed dependencies. Moreover performing similar systematic studies in humans would be of great value in the clinical settings and can address uncertainties associated with ventilation parameters and their effects on ADC measurements.

Acknowledgements: This work was supported by NIH grants R01-HL64741, R01-HL077241, and P41-RR02305. **Reference:** [1] Denny E, Schroter RC. A model of non-uniform lung parenchyma distortion. J Biomech. 2006;39(4):652-63.