Regional Ventilation Mapping of the Rat Lung Using Hyperpolarized ^{3}He and ^{129}Xe Magnetic Resonance Imaging

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***Introduction*:** With the addition of inhaled contrast agents, namely hyperpolarized ^{3}He and ^{129}Xe, Magnetic Resonance (MR) imaging has the ability to measure anatomical and functional changes associated with disease progression in the rodent lung. Functional changes are expected to be strong early indicators of obstructive lung disease (e.g. asthma) progression and regression with therapy. In this work, hyperpolarized ^{3}He and ^{129}Xe MR imaging was used to measure regional ventilation in the normal rat lung using the dynamic gas signal from inside the lungs (1). This method used a variable flip angle approach (FAVOR) to mitigate the effects of RF pulses and relaxation both in the ventilator system and in the rat lung. A theoretical model was used to fit signal enhancement curves on a pixel-by-pixel basis to generate two-dimensional maps of the ventilation parameter, r, which was defined as the fractional refreshment of gas per breath. Regional ventilation has been previously measured in normal rats using xenon-enhanced computed tomography (CT) and hyperpolarized ^{3}He MR (2). These methods have demonstrated agreement in the measurement of whole-lung ventilation, but some difference in ventilation gradients in the superior/inferior (S/I) direction. In order to determine if this difference is due to the imaging technique and/or the physiological distribution of the two gases, it is desirable to perform ventilation mapping with hyperpolarized ^{129}Xe MR. In the present study, ventilation was measured using both hyperpolarized ^{3}He and ^{129}Xe MR in the same animals under similar conditions of ventilation. Ventilation gradients were calculated for both the superior/inferior (S/I) and anterior/posterior (A/P) directions and compared between the two methods.

***Methods*:** *This study was approved by the University of Western Ontario Council on Animal Care*. Healthy male Sprague-Dawley rats (n = 2, ~440 g) were anesthetized and ventilated in the supine position following intubation. Rats were ventilated with the following settings: respiratory rates of 60 breaths/min for air and 30 breaths/min for ^{3}He or ^{129}Xe, peak inspiratory pressure (PIP) of 12 cm H_2O, tidal volume of 3.5 mL, and inspiratory/expiratory time ratio of 1:1.4 for normal air breathing. ^{3}He or ^{129}Xe gas was placed in a pressurized reservoir, and tidal volumes were controlled by maintaining the reservoir at a constant pressure (12 – 15 cm H_2O). The ventilator system contained a pneumatic valve assembly, which allowed for rapid computer-controlled switching between air and the contrast agent in the pressurized reservoir (1). Imaging experiments were performed at 3.0 T (GEHC, Waukesha, WI) with a high-performance insert gradient coil, and two separate transmit-receive bird-cage coils tuned to the appropriate ^{3}He and ^{129}Xe resonant frequencies. Following the FAVOR method (1), single-slice 2D projection images were obtained using a fast VFA gradient-echo method (FOV = 5 cm, N_x = 64, N_y = 64) triggered by the ventilator following each breath of contrast (8 breaths, ~1 s breath-hold). ^{3}He imaging used TE = 0.6 ms and TR = 2.5 ms, while ^{129}Xe imaging used TE = 2.0 ms and TR = 14 ms. After image segmentation, the ventilation parameter, r, was estimated for each voxel by fitting signal enhancement curves according to the method of Santyr *et al*. (1). The FAVOR method was performed in both the coronal and axial planes, allowing for the calculation of ventilation gradients in the superior/inferior (S/I) and anterior/posterior (A/P) directions. To calculate ventilation gradients, a 2D map of ventilation data was averaged to form a one-dimensional projection in the direction of interest. A linear regression was performed for the 1D projection, and the slope of the regression yielded the ventilation gradient.

Table 1: Summary of r values and ventilation gradients for all rats

Rat	^{3}He			^{129}Xe		
	r ± SD	S/I [cm^{-1}]	A/P [cm^{-1}]	r ± SD	S/I [cm^{-1}]	A/P [cm^{-1}]
1	0.38±0.10	0.147±0.001	-0.0389±0.0001	0.33±0.03	0.091±0.001	-0.014±0.001
2	0.42±0.02	0.0099±0.0001	-0.1055±0.0001	0.38±0.12	0.040±0.001	-0.021±0.001

***Results*:** Figure 1 shows representative r maps, calculated for the same rat using ^{3}He (a) and ^{129}Xe (b), respectively. Since large r values in the major airways would distort the calculation of ventilation gradients in the lung parenchyma, the major airways were removed from ^{3}He r maps prior to calculating ventilation gradients. Table 1 summarizes the whole lung r values and ventilation gradients calculated for the S/I and A/P directions using both ^{3}He and ^{129}Xe. Typical ventilation gradients are shown in Figure 2 for the S/I direction using ^{3}He (a) and ^{129}Xe (b), respectively. These plots show a 1D projection in the S/I direction, with linear regression indicating the ventilation gradient.

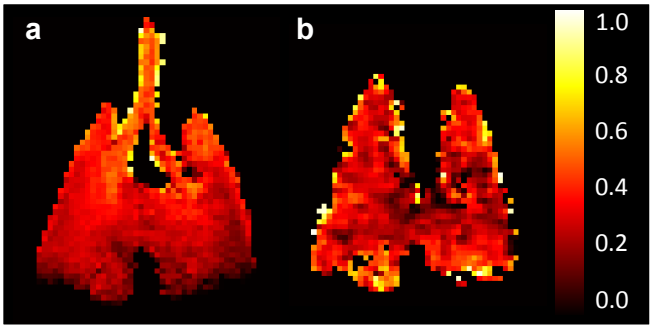

Figure 1: Calculated 2D coronal projection r maps obtained for (a) ^{3}He and (b) ^{129}Xe in the same rat.

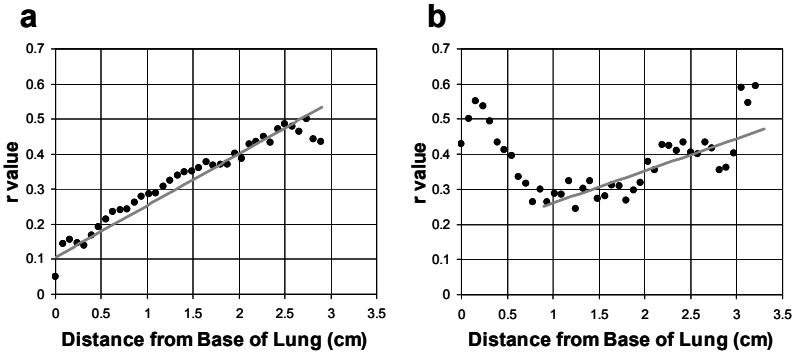

Figure 2: Ventilation gradients calculated in the superior/inferior (S/I) direction for (a) ^{3}He and (b) ^{129}Xe in the same rat.

***Discussion*:** Whole lung estimates of ventilation are in agreement with the geometrical value based on the estimated total lung capacity (TLC) and known ventilator tidal volume. The ventilation gradient calculated for the A/P direction for ^{3}He and ^{129}Xe MR is in reasonable agreement with previous measurements performed using xenon-enhanced CT (3). The negative value implies greater ventilation in more dependent regions of the lung. The ventilation gradients calculated in the S/I direction for ^{3}He and ^{129}Xe MR agree with previous ^{3}He MR results (2). This confirms that ^{129}Xe may be a suitable replacement for ^{3}He in ventilation mapping of the lung, especially considering that ^{3}He is an exceedingly rare isotope and unavailable in sufficient quantity for wide-spread clinical use. It is interesting to note that ventilation gradients obtained with ^{3}He and ^{129}Xe MR in the S/I direction do not agree with previous xenon-enhanced CT results (2). This finding suggests that differences in S/I ventilation gradients calculated from MR and CT were due to the type of image acquisition and not the type of inhaled gas. In the future, these imaging techniques will be extended to 3D acquisition in order to measure ventilation gradients in all three dimensions simultaneously (i.e. S/I, A/P and R/L). These studies will be performed in both healthy rats and those with airway narrowing to simulate asthma (4). Overall, regional ventilation mapping using hyperpolarized noble gas contrast agents is expected to significantly improve our understanding of breathing physiology and pathophysiology.

References*:** [1] **Santyr *et al., *Magn Reson Med* 59:1304–1310, 2008. [2] **Santyr *et al***., *NMR in Biomed* (accepted) 2010. [3] **Lam *et al***., *J Appl Physiol* 103: 1848–1856, 2007. [4] **Bates *et al***., *J Appl Physiol* 100:500–506, 2006.

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