

Reproducibility and Volume-dependency of Regional Measurements of Lung Ventilation by Hyperpolarized 3He MRI

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INTRODUCTION: Pulmonary ventilation is an important marker in lung physiology and is sensitive to many obstructive and restrictive pulmonary diseases. Conventional techniques for measuring regional ventilation are based on delivery/clearance rates of radioactive gases, as well as xenon-contrast X-ray CT. Hyperpolarized ³He MRI has emerged as a novel technique with unique capabilities for visualization of ventilated airspaces noninvasively. In this work we assess the reproducibility of measurements and their dependency on the administered volume using a serial ventilation sequence developed earlier [1].

METHODS: The animal experiment was conducted using a healthy male Sprague-Dawley rat (350 g body weight) in accordance with protocols approved by IACUC of the University of Pennsylvania. The rat was sedated with a 0.1 g/kg IP ketamine and 10 mg/kg xylazine, repeated every 90 minutes and was intubated with a 27-long, 14G angiocatheter modified with a sealant enabling a breath-hold of up to 25 cm H₂O for 5 seconds with negligible leakage. Spontaneous respiration was temporarily suppressed using 1 mg/kg IV of pancuronium bromide while connected to the mechanical ventilator. Ventilation was maintained at $V_T = 1$ ml/100g body weight @ 60 BPM. The animal was placed supine in the coil. Heart rate and blood oxygen saturation level were continuously monitored and temperature was maintained at 37°C using a flow of warm air. Imaging was performed on a 50-cm 4.7-T MRI scanner equipped with 12-cm 25 G/cm gradients and a quadrature 8-leg birdcage body coil (152.95 MHz, ID=7cm) using a GEMS imaging pulse sequence with FOV=6×6cm², ST=4mm, $\alpha=4-5^\circ$, MS=64×64 pixels, $T_R=6.6$ ms and $T_E=3.3$ ms. The trachea was included in the selected middle slice. Fractional ventilation, r_A , was measured according to the serial ventilation sequence technique [1] using $N=10$ HP ³He breaths. The concentration of the administered HP gas was controlled with the ventilator at ³He:O₂ ≈ 4:1. Regional distribution of flip angle, α , was estimated in the imaged body by acquiring a series a back-to-back images with identical imaging parameters to ventilation imaging sequence with no interscan time delay and during a single breath-hold. This calculation is based on the assumption that RF-induced depolarization is the dominant decay mechanism for HP ³He in the time scale of image acquisition, compared to oxygen-induced decay or other *in vivo* T₁ relaxation. The intrasubject reproducibility of fractional ventilation measurement was assessed by calculating intravoxel variation of the calculated r_A value across three consecutive measurements. The mean coefficient of variation of r_A , $\sigma(r_A)/\mu(r_A)$ was then reported as a measure of technique reproducibility over the entire lung. Pairwise comparison between results obtained under different conditions (e.g. with two different ventilation sequences and with identical tidal volumes) was performed using a voxel-by-voxel linear regression analysis between the two fractional ventilation maps and by calculating the corresponding regression coefficient.

RESULTS: Reproducibility of measurements were assessed by repeating the measurement three times using $V_T = 3$ ml in one imaging session. Figure 1.b shows the voxel-by-voxel coefficient of variation the measured r_A value as a percentage, $CoV(r_A) = \sigma(r_{A,i})/\mu(r_{A,i})$ for the i -th voxel across the three measurements. The average $CoV(r_A)$ in this healthy rat was measured as $8.9 \pm 8.0\%$. In addition the pairwise spatial correlation of each two sets of measurements were evaluated. Also shown is the voxel-by-voxel correlation assessment of the first and second r_A measurements in the rat lung with a relatively linear regression coefficient of $R^2 = 0.94$. As it is evident from the scatter plot, the dispersion of datapoints become larger for higher r_A values. Fractional ventilation measurements were also performed on the same rat using four different tidal volumes, $V_T = 2, 3, 4$ and 5 ml. As anticipated, a larger tidal volume yields a distribution of regional fractional ventilation with an elevated mean r_A value. Figure 1.a shows, for each tidal volume, an example MR image of the rat lung along with the corresponding fractional ventilation map and the frequency distribution histogram. The overall enlargement of lung is apparent in the MR images. For comparing r_A mean and standard deviation values in each measurement, voxels with a near unity r_A value (corresponding to conductive airways) were excluded from the distribution. Calculated values at the four V_T (2, 3, 4 and 5 ml) were as follows: 0.42 ± 0.21 , 0.49 ± 0.16 , 0.63 ± 0.16 , and 0.69 ± 0.15 , respectively. Histograms also move to the right with increasing tidal volumes. Fractional ventilation in regions closer to major bronchi increase to a larger degree with increased tidal volume, compared to distal regional of lung parenchyma.

DISCUSSION:

The repeatability of *in vivo* measurements was assessed in a healthy rat lung and voxel-by-voxel variation was measured at less than 10%. In addition results were shown to tightly correlate ($R^2 = 0.94$) across different measurements. This level of precision is strongly dependent on maintenance of a reproducible tidal volume as controlled by the mechanical ventilator. As is clear from the figure, any misestimation of V_T can have a drastic effect on the measured r_A value. This observation highlights the importance of normalizing and accurate titration of tidal volumes, especially when using this measurement technique for intersubject comparison.

REFERENCES: [1] Emami K, et al. A Novel Approach to Measure Regional Lung Ventilation Using Hyperpolarized 3He MRI – Potential in Clinical Studies; ISMRM 16th Scientific Meeting, Berlin, Germany: May 2007.

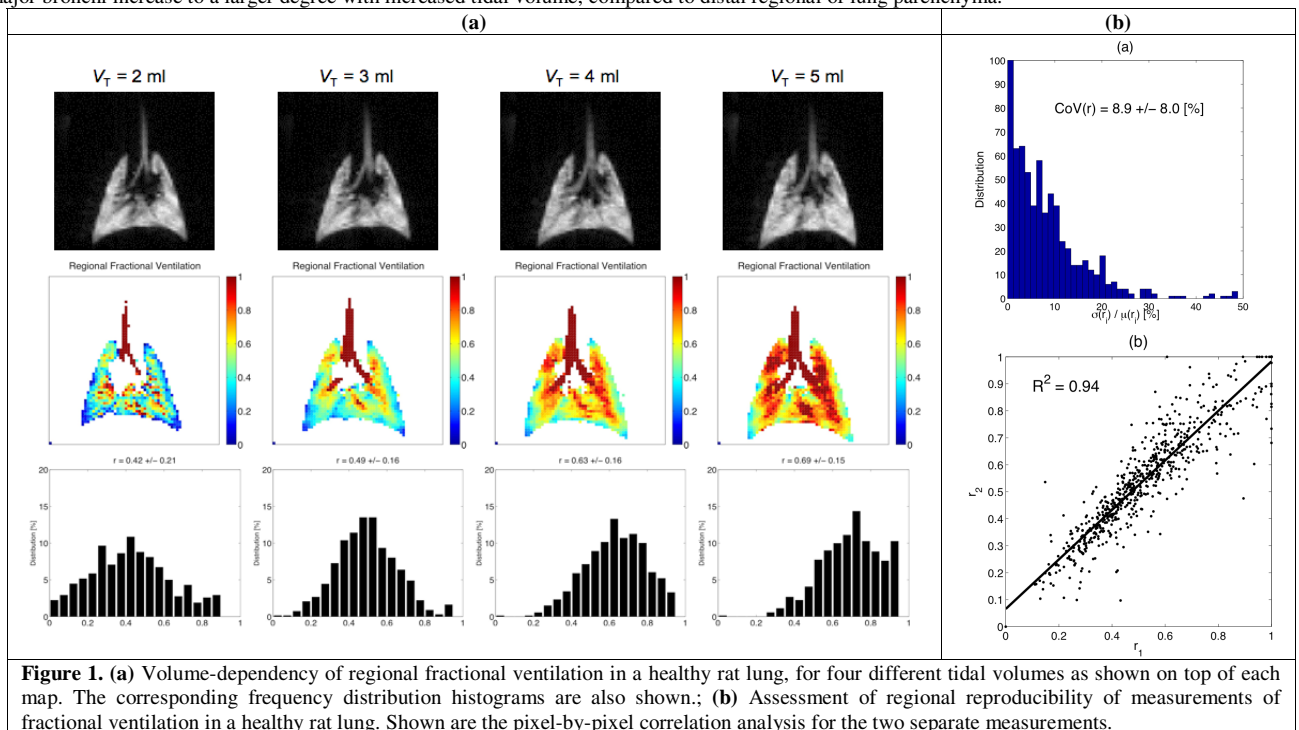


Figure 1. (a) Volume-dependency of regional fractional ventilation in a healthy rat lung, for four different tidal volumes as shown on top of each map. The corresponding frequency distribution histograms are also shown.; **(b)** Assessment of regional reproducibility of measurements of fractional ventilation in a healthy rat lung. Shown are the pixel-by-pixel correlation analysis for the two separate measurements.