Quantification of Regional Lung Microstructure Response to Positive End-Expiratory Pressure by Hyperpolarized Gas MRI in Surfactant-Deficient Rats

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INTRODUCTION: Surfactant deficiency causes atelectasis and predisposes subjects to ventilator associated lung injury (VALI). This phenomenon also occurs in mechanically ventilated animal models by causing abnormalities in alveolar geometry and mechanics. Positive end expiratory pressure (PEEP) has shown to attenuate VALI. For this reason, its clinical use is advocated as a means to improve the outcomes of ventilated patients who experienced atelectasis. However, standard physiological and radiological measurements do not elucidate the exact mechanisms linking atelectasis and VALI, mostly due to their inability to assess airspace morphology and regional lung mechanics. Hyperpolarized (HP) gas MRI allows to measure the apparent diffusion coefficient (ADC) of ^{3}He within the acinar airspaces, including the alveoli and the respiratory bronchioles. This enabling technology may also be used to estimate changes in the size of these airspaces during mechanical ventilation. In this project, we aimed at (1) using HP ^{3}He diffusion MRI to investigate the effects of surfactant deficiency on alveolar geometry and mechanics in ventilated rats, and (2) assessing the effects of varying PEEP levels on airspace size. For this purpose rat lungs were imaged with HP ^{3}He diffusion MRI before and after induction of surfactant deficiency by pulmonary saline lavage (SL).

METHODS: Male Sprague-Dawley rats (n=3, BW=300±50g) were anesthetized with pentobarbital, temporarily paralyzed with pancuronium, intubated, and mechanically ventilated by a custom small-animal MR-compatible ventilator with a delivery accuracy of ±100µL/breath. Rats were breathing a mixture of ^{4}He:O_2 (4:1) at 60 BPM and I:E=1:2, at a nominal V_T=10ml/kg. The animal's peak inspiratory pressure (PIP) was continuously monitored and recorded by a high-precision MR-compatible optical pressure transducer (Samba Sensors AB). PEEP was increased from ZEEP (0 cmH_2O) to 9 cmH_2O, in 3 cmH_2O steps. Each level of PEEP was maintained for a period of 5 minutes. Then, SL was performed by instillations of 30 ml/kg saline (37±2ºC), repeated until a goal arterial oxygen saturation of no larger than 90% was reached and remained unchanged. After a period of stabilization of at least 20 min, PEEP was increased from 0 to 21 cmH_2O in 3 cmH_2O steps, maintained for 5 minutes at each level. At the end of each PEEP period, ^{3}He ADC and the peak inspiratory pressures (PIP) were measured. For ADC imaging rats were ventilated with five identical breaths of HP ^{3}He:O_2 (4:1) at the designated PEEP level followed by a 3-sec breath-hold during which five diffusion-weighted images were acquired corresponding to b-values = 0.00, 3.73, 2.18, 1.00 and 0.00 s/cm^2. This procedure was repeated immediately with identical but reversed polarity diffusion gradient b-values. These 10 diffusion-weighted images were then combined to yield the ADC map of the imaged slice according to a double-acquisition diffusion imaging scheme described earlier [1]. Images were acquired using a diffusion-weighted gradient echo imaging pulse sequence with centric phase-encoding in a 50-cm bore 4.7-T MRI scanner (Varian Inc) equipped with a 12-cm, 25-G/cm gradients and a 2-3/4"-ID quadrature 8-leg birdcage body coil (Stark Contrast). Images were acquired in the middle transverse slice of the rat lung with the following imaging parameters: FOV=6×6cm^2, ST=20mm, MS=64×64, α=4~5°, TR=6.6ms, and TE=4ms. Diffusion sensitizing gradient was applied along the phase-encoding (L–R) direction with the following timing parameters: Δ=1ms, δ=200μs, and τ=180μs according to the naming convention of [2].

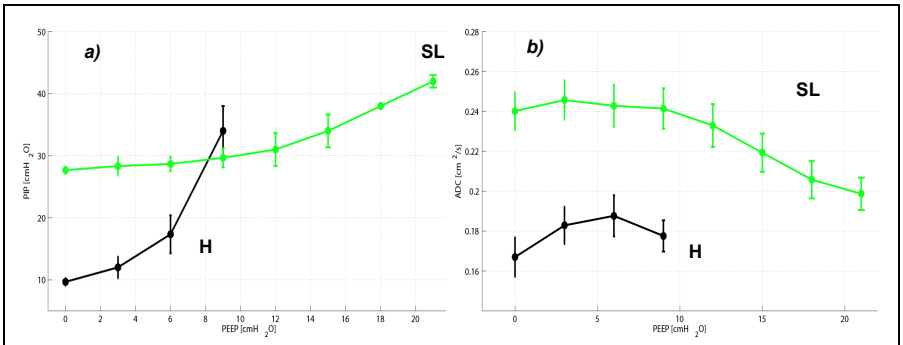

Figure 1: mean and SD values for a) PIP and b) ADC measured before (H) and after (SL) performing saline lavage at various levels of PEEP

RESULTS AND DISCUSSION: SL caused significant atelectasis, as suggested by the increase in PIP observed at ZEEP, compared with pre-SL conditions, as shown in **Figure 1(a)**. SL increased the values of ADC at all levels of PEEP and particularly at ZEEP, as shown in **Figure 1(b)**. Representative ADC maps corresponding to zero, low and high PEEP levels are shown in **Figure 2** for one animal pre- and post-SL, showing an overall increase in mean ADC values and in the post-SL heterogeneity of ADC distribution, compared to pre-SL. This effect is most likely due to redistribution of inspired gas from the atelectatic lung to ventilated airspaces, mostly comprised of non-collapsed alveoli. Gas redistribution due to atelectasis is probably the main factor in the generation of VALI in surfactant-deficient lungs, due to the resulting alveolar overdistension. Before SL, ADC increased with PEEP, reaching a maximum at PEEP = 6 cmH_2O, corresponding to a PIP of approximately 20 cmH_2O, as shown in **Figure 1(b)**. This pattern of response is compatible with increasing alveolar size caused by the raising airway pressures. The limit to ADC increase at higher PEEP could be explained by restrained alveolar wall distension imposed by the interstitial collagen scaffold, also resulting in the observed sharp increase in PIP, as shown in **Figure 1(a)**. The response of ADC to PEEP was significantly modified by SL: increasing PEEP caused a progressive drop in mean ADC despite an increasing PIP, shown in **Figure 1(b)**. ADC in the imaged slice shows a tendency toward lower and more homogenous distribution while PEEP was elevated, as shown in **Figure 2**. This response could be explained by on-going recruitment of atelectatic alveoli, causing a favorable redistribution of inspired gas towards newly reopened airspaces. This response could also explain the beneficial effects of PEEP under surfactant deficiency. The recruitment of a quota of atelectatic parenchyma may also explain the small decrease in ADC observed at the highest PEEP prior to SL.

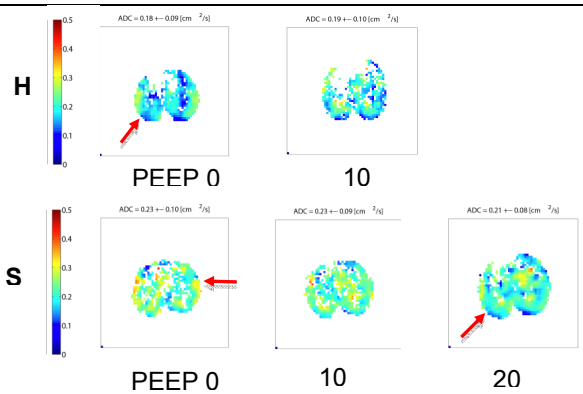

Figure 2: Representative ADC maps obtained in one rat before (H) and after (SL) saline lavage at various levels of PEEP.

CONCLUSIONS: As of today, HP ^{3}He MRI is the only radiological technique providing direct, non-invasive estimates of the morphology and the mechanics of airspaces at the acinar level. Measurements of ADC can potentially elucidate the mechanisms of VALI, verify the existence of hypothetical models of lung behavior, and document the effects of PEEP and other ventilator maneuvers. This technique can potentially be adopted as an investigational tool to explore other models of lung injury and to verify the extrapolations of experimental findings to human diseases.

REFERENCES: [1] Emami, K, *et al.* Proc Intl Soc Mag Reson Med 2007; [2] Yu, J, *et al.* J Magn Res Imag 2007.