Effects of Ventilator Induced Lung Injury on Airspace Distension and Regional Ventilation in Rats Using Hyperpolarized MRI

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INTRODUCTION: Acute lung injury (ALI) is a form of respiratory failure that has high mortality. Survival in patients with ALI worsens when it is compounded by iatrogenic ventilator induced lung injury (VILI), but the ideal strategy of lung protection remains elusive. Research has identified airspace over-distension and stress as key components that contribute to VILI. However, airspace dimensions and dynamic ventilation patterns cannot be assessed by conventional imaging and monitoring methods, which limits the progress of respiratory therapy. Hyperpolarized (HP) ^{3}He MRI, as a non-invasive imaging technique, has demonstrated sufficient sensitivity to detect these changes. In this study, we assess changes of two HP ^{3}He MRI-based measurements of gas diffusivity (a measure of lung structure) and ventilation (a measure of lung function) after the induction of VILI through high tidal volume (HV) ventilation in previously healthy rats. Our hypothesis is that the combination of lung function and structure measurements will be effective at evaluating progressive changes in the lung due to VILI. These measurements will also illustrate the effects of positive end-expiratory pressure (PEEP) and other lung protective strategies on lung mechanics and dynamics at the level of the peripheral airspaces.

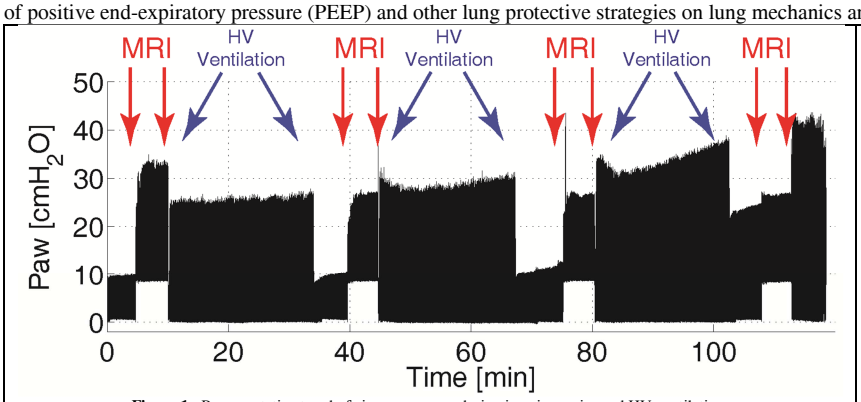

Figure 1. Representative trend of airway pressure during imaging series and HV ventilation.

	Healthy baseline				VILI					
	PEEP 0		PEEP 9		PEEP 0		PEEP 9			
	ADC (cm^2/s)	*r*	ADC (cm^2/s)	*r*	ADC (cm^2/s)	*r*	ADC (cm^2/s)	*r*	V_T (ml/kg)	Injury Onset (min)
Rat #1	0.19	0.48	0.21	0.31	0.24	0.63	0.25	0.39	30	90
Rat #2	0.18	0.59	0.2	0.26	0.25	0.78	0.25	0.64	35	40
Rat #3	0.16	0.34	0.17		0.23	0.79	0.23		35	30
Rat #4	0.18	0.39	0.21	0.2	0.24	0.59	0.24	0.39	35	35
Mean	0.18	0.45	0.2	0.26	0.24‡	0.70‡	0.24‡	0.47‡	‡: P < 0.001	
STD	0.01	0.11	0.02	0.06	0.01	0.1	0.01	0.14		

Table 1. Individual values and mean ± STD of ADC and r, measured before and after VILI induction by high V_T ventilation.

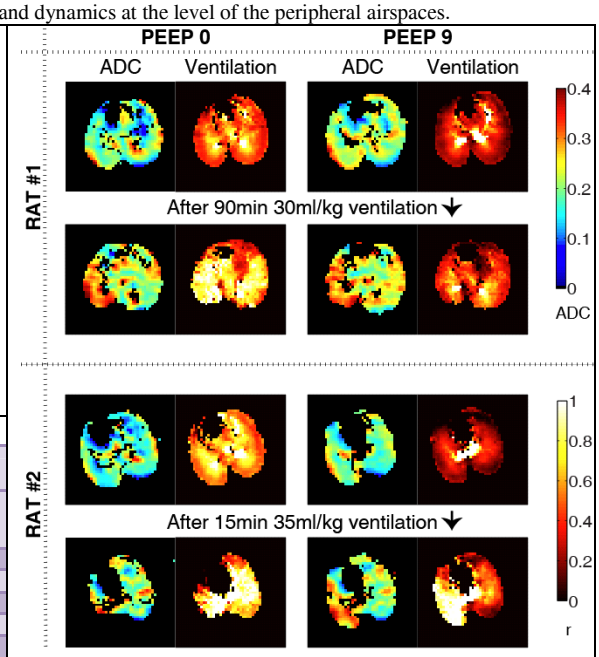

Figure 2. Maps of ^{3}He ADC and fractional ventilation at ZEEP and PEEP 9 cmH_2O obtained at baseline condition and after HV ventilation in two representative animals.

METHODS: 4 healthy Sprague-Dawley rats (body weight=330±40g) were utilized in this study. During imaging, the rats were anesthetized, intubated, paralyzed, and mechanically ventilated by a small-animal MR-compatible ventilator with a volume delivery accuracy of ±100μL/breath. The rats were breathing a mixture of ^{4}He:O_2 (4:1) at 60 BPM and I:E=1:2 at a tidal volume (V_T) of 10ml/kg. Each animal's airway pressure (Paw) was continuously monitored and recorded by a MR-compatible optical pressure transducer. Before starting the imaging process, the rats underwent an alveolar recruitment maneuver that used a stepwise sequence of positive end-expiratory pressure (PEEP) levels to minimize the effect of atelectasis during imaging [1]. Rats then underwent HV ventilation with 50% inspired O_2 at 30 BPM, at either V_T of 30 or 35 ml/kg. As **Figure 1** shows, the Apparent Diffusion Coefficient (ADC) and fractional ventilation images at zero PEEP (ZEEP) and PEEP=9cmH_2O were obtained every 5 minutes for 35ml/kg rats and every 15 minutes for 30ml/kg rats. For ADC imaging, rats were ventilated with five identical breaths of HP ^{3}He:O_2 (4:1) followed by a 5-sec breath hold. A diffusion sensitizing gradient was applied along the phase-encoding (L–R) direction with the following timing parameters: Δ=1ms, δ=200μs, and τ=180μs. Fractional ventilation was measured as described previously in [2]. Images were acquired in the transverse slice right below the heart with the following imaging parameters: FOV=6×6cm^2, ST=10mm, MS=64×64, α=4~5°, TR=6.6ms, and TE=4ms.

RESULTS AND DISCUSSION: As shown in **Figure 2** and in **Table 1,** at healthy baseline ADC increased at PEEP 9 compared to ZEEP due to the expansion of ventilated airspaces by higher airway pressures [3]. Fractional ventilation, however, decreased as the increases in functional residual capacity and airspace size altered alveolar kinetics. HV induced VILI, as documented by histology and lung computed tomography showing severe lung tissue inflammation with atelectasis (data not shown). In all animals, VILI resulted in a significant increase in ADC signal at ZEEP **(Table 1)** along with an increase in focal heterogeneity **(Figure 2)**. This finding was likely due to the over-distension of residual aerated airspaces caused by atelectasis and edema of a significant amount of lung tissue. VILI also caused marked increases of fractional ventilation at ZEEP **(Table 1)**, which were approximately located in the same areas of ADC elevations **(Figure 2)**. This result may be related to the concentration of ventilation in a reduced number of residual aerated (non-atelectatic) airspaces. The observed radiological changes were time-dependent and were more rapid in animals ventilated with the higher HV value. For example, Rat #1 with 30ml/kg HV ventilation was injured after 90 minutes, but the onset of VILI occurred after only 15 minutes for Rat #2 ventilated with 35ml/kg **(Figure 2)**. Additionally, the response to PEEP was also affected by HV values as ventilation in Rat #1 was somehow recovered at high PEEP, possibly due to recruitment in previously atelectatic airspaces. In contrast, in Rat #2, ventilation was not affected by PEEP, which was probably due to the presence of more severe injury and poor recruitability.

CONCLUSION: HV ventilation caused VILI in a volume- and time-dependent manner. Changes induced by VILI were detected by HP MRI as regional increases of ADC and fractional ventilation. These results can be explained by the numeric loss of ventilated airspaces due to pulmonary edema and atelectasis, and were partially reversible by the use of PEEP, depending on injury severity. Areas of high ADC and hyperventilation are likely to represent regions of focally increased lung stress and over-distension, which are at risk of further worsening of injury. This pilot study suggests that HP MRI is an innovative, non-invasive radiological instrument which may have a role in the investigation of the effects of mechanical ventilation on lung biology and in the study of lung protective strategies.

REFERENCES: [1] Cereda et al., *J. Appl. Physiol.* 110, 499-511 (2011). [2] Emami et al. *Magn. Reson. Med.* 63, 137-150 (2010). [3] Cereda et al. *Crit. Care Med (in press)*