Assessment of Longitudinal Changes of Lung Function and Structure Pre– and Post– Lung Volume Reduction Surgery in a Rat Elastase Model of Emphysema

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INTRODUCTION: Emphysema is a form of chronic obstructive pulmonary disease; it has a high mortality rate and is associated with significant morbidities. Few medical therapies are effective at ameliorating symptoms, and supplemental oxygen therapy plays an important role in managing advanced cases. Lung volume reduction surgery (LVRS) is a surgical strategy for improving lung function in advanced forms of emphysema. During surgery, approximately 30% of the most diseased portion of the lung is removed returning the thoracic cavity to a more normal and efficient size. Selection strategies and mechanisms by which lung function improve are important and interrelated topics of study in LVRS. Of interest is whether respiratory mechanics can be improved even in homogenous forms of emphysema. We hypothesize that respiratory mechanics should improve in homogenous forms of emphysema due to reposition the diaphragm to a more mechanically favorable position after lung volume reduction. We test this hypothesis through a longitudinal cohort study of homogeneously induced emphysematous rats undergoing LVRS and sham surgery. Metrics of emphysema and lung function are provided by hyperpolarized (HP) ^{3}He MRI methods. The implications of these findings may play a role in defining future patient selection criteria.

METHODS: All experiments were conducted in accordance to an approved IACUC protocol. HP ^{3}He MRI was performed on a group of healthy and a severely emphysematous rats, pre– and post–LVRS. Emphysema was induced in male Sprague-Dawley rats by a single intratracheal instillation of 25U/100g of porcine pancreatic. The healthy cohort, with similar physiological conditions was kept in same environment. At 10 months after elastase induction, both cohorts underwent pulmonary function tests in a plethysmographic maneuver system. PFT was followed by MRI session during which regional fractional ventilation and apparent diffusion coefficient of ^{3}He were measured in rat lungs. For imaging, rats were intubated using a 14-gauge angiocatheter and induced with ketamine and xylazine anesthesia, temporarily paralyzed with pancuronium bromide, and ventilated using an MRI compatible ventilator, while vital signs being monitored at a tidal volume = 15% TLC, 60 BPM and I:E=1:2. Imaging was performed on a small-bore 4.7-T animal scanner (Varian Inc., Palo Alto, CA) using a home-made 12-leg birdcage coil tuned to ^{3}He frequency of 152.95 MHz. HP ^{3}He was generated via spin-exchange optical pumping method using a commercial polarizer (GE Healthcare, Durham, NC). Helium images were obtained during a breath-hold using a multi-slice gradient echo imaging pulse sequence with the following parameters: FOV=6x6cm^2, number of slices=3, slice thickness=6mm, inter-slice gap=0.5mm, flip angle=4~5°, matrix size=64x64 pixels, T_R=4.1ms, and T_E=2.1ms. Diffusion images were acquired using a diffusion-weighted gradient echo pulse sequence with diffusion time Δ=1ms, and b-values = 0.00, 3.41, 2.00, 0.91, and 0.00 s/cm^2. Fractional ventilation was measured using incremental build-up of HP ^{3}He signal in the lung by acquiring an image at the end of each polarized gas breath as described earlier [1], for 10 HP breaths. Two weeks after imaging half of the population of both cohorts underwent LVRS, and sham surgery was performed on the remaining animals. For LVRS rats were anesthetized, intubated, and ventilated (CWE Inc, Ardmore, PA) as they underwent median sternotomies. The upper lobes of the lungs were resected and the stumps were ligated. IV catheters were placed in each hemithorax at a –2 cm-H_2O suction until extubation. Two weeks after the surgery, identical PFT and MRI procedures were performed on the animals. For animals with stable physiological conditions the measurements were performed again at a time interval of two weeks. Data analysis was performed using STATA.

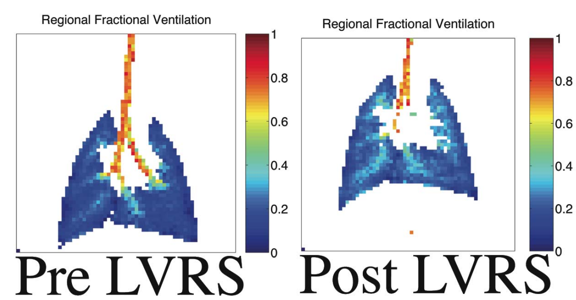

Figure 1. Fractional ventilation images pre and post LVRS, showing coronal slice through trachea.

	<r>	<ADC>	TV (ml)
LVRS pre	0.13	0.08	3.8
LVRS Post	0.22	0.08	3.6
Sham pre	0.22	0.08	3.5
Sham post	0.18	0.09	3.5

Table 1. Sample LVRS rat vs Sham rat used in comparison. Means for individual rats not cohorts.

RESULTS AND DISCUSSION: Sample pre and post LVRS fractional ventilation images are shown in figure 1. Note how the diaphragm appears to be more flat in the pre LVRS case and that the fractional ventilations improve, i.e., increase both globally as well as regionally and that this increase is uniformly distributed throughout the lung fields. Table 1 shows fractional ventilation, ADC, and tidal volumes used for imaging for the rat in figure 1 and a sample sham rat for comparison. Note the improvement in mean fractional ventilation and despite the decrease in resting tidal volume. Also note how mean ADC values are not affected by the surgery. MANOVA testing was used to show that pre and post surgical fractional ventilations were statistically different at α=0.05, while the ADC mean vectors were not. Subsequent ANOVA testing with bonferroni control of alpha error were indicated and paired tests shows that post LVRS fractional ventilations are larger than pre treatment ($p<0.05$), and that changes in mean fractional ventilation values in the sham surgery and LVRS cohorts are different, namely because there is a statistically significant decrease in fractional ventilation post sham surgery. This decrease is small.

Conclusion: Fractional ventilation increases in homogenous forms of emphysema after LVRS while it decreases after sham surgery. The ADC is not affected by surgery. Suggesting that improvements in lung function are independent of the lung's microstructure. These findings also suggest that LVRS may be applicable to a broader class of patients than previously though.

REFERENCE: [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.