Early Detection of Emphysema By Hyperpolarized Helium-3 MRI Through Measuring Regional Fractional Ventilation

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Introduction: Emphysema, a chronic obstructive lung disorder, is characterized by the progressive destruction of the lung parenchyma, leading to loss of surface area for gas exchange, reduction in lung elastic recoil, and irreversible airflow obstruction. Sensitive markers of disease progression capable of detecting the earliest forms of emphysema are important for the study and treatment of this entity. Regional measures of fractional ventilation are sensitive at detecting severe cases of emphysema [1]. This work attempts to assess the sensitivity of this technique for time progression of this disease as well as at different severity levels.

Methods: In order to assess the sensitivity of regional fractional ventilation for early changes in lung function and structure, and milder forms of the disease, two groups of male Sprague-Dawley rats (~400±25g) were induced with elastase. Experiments were conducted in accordance to an IACUC approved protocol. The first group was exposed to a 5U/100g dose of porcine pancreatic elastase, corresponding to *mild* emphysema, and the second group was exposed to 10U/100g, corresponding to *moderate* emphysema, as opposed to 20~25U/100g commonly accepted for *severe* case of this disease model. These two groups were then imaged at two different time points, namely 5 and 10 weeks after the induction, which along with a group of normal healthy rats formed a total of five subgroups.

The animal's pulmonary parameters including tidal volume (TV) = 2.7~3.6 ml, respiratory rate (RR) = 66~98 BPM and inspiration/expiration time ratio (I%) = 36~55% were measured on an unrestrained plethysmographic measurement system (Buxco Electronics, Wilmington, NC) on the same day of imaging. These parameters were then used to normalize the mechanical ventilation parameters. For imaging, rats were intubated with a 14-gauge angiocatheter and maintained on IP xylazine and ketamine anesthesia, paralyzed with pancuronium, and ventilated using an MRI compatible small animal ventilator (GE Healthcare, Durham, NC) while vital signs and temperature were monitored for the entire duration of study. Imaging was performed on a small-bore 4.7-T animal magnet (Varian Inc., Palo Alto, CA) using a 12-leg birdcage coil tuned to ^{3}He frequency of 152.95 MHz. The hyperpolarized ^{3}He was generated via the spin-exchange optical pumping method with the use of a commercial polarizer (GE Healthcare, Durham, NC). The helium images were obtained during a breath-hold using a multi-slice fast gradient echo imaging pulse sequence with the following parameters: FOV = 5 cm x 5 cm, slice thickness (ST) = 4 mm, flip angle= 10 degrees, matrix size= 128 x 128 pixels, TR/TE= 6.6/3.3 ms.

Regional fractional ventilation (*r*) was measured using incremental build-up of hyperpolarized helium signal as described earlier [1]. Upon completion of imaging, each animal was sacrificed. Slides of four axial tissue sections were made from the central portion of each lobe (left, right upper, right middle and right lower) and stained with hematoxylin and eosin. For each section, Mean Linear Intercept (Lm [μm]) was calculated as a measure of alveolar size, and thus the degree of emphysema, and to study the correlation with fractional ventilation in respective subjects. This way 48 different values were calculated for each animal. The average reciprocal of these values was then extracted as the representative Lm for each animal.

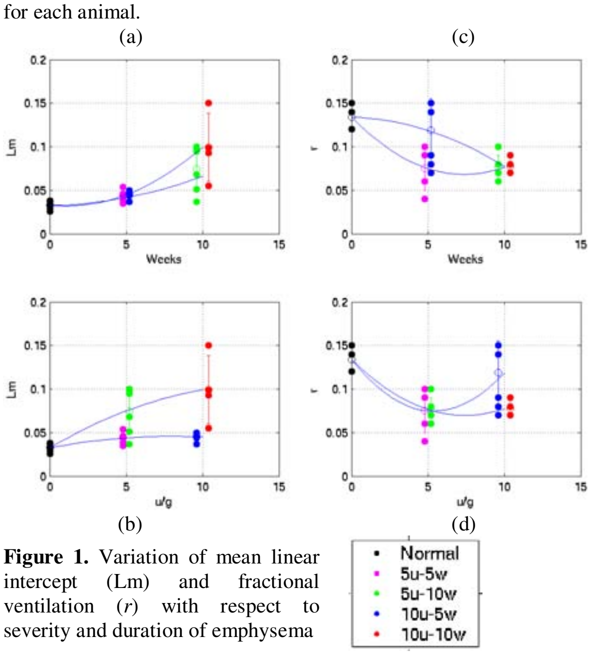

Figure 1. Variation of mean linear intercept (Lm) and fractional ventilation (*r*) with respect to severity and duration of emphysema

Results and Discussion: The average Lm and *r* measurements for all subjects of five groups are summarized in Figure 1. The individual data points for subjects in each group are shown with different colors, along with their respective standard deviations as vertical bars. All behaviors are modeled as quadratic time and dose functions, yielding minimum error in curve fits. As expected, the mean linear intercept increases with both a higher dose and the evolution of time, although at different rates (Figure 1(a) and Figure 1(b)). Regional fractional ventilation in both mild and moderate emphysema drops monotonically with time (Figure 1(c)). Even though *r* approaches a similar value for both doses of elastase over the 10-week period, it shows a broader difference during early stages of disease, i.e. around 5 weeks. Lm difference is almost undistinguishable for these two levels of severity at the 5-week time point. This difference could be caused by presence of edema in alveoli in the transitional state of this disease model, giving rise to a higher intersubject variability. Also as evident in Figure 1(d), mild emphysema shows a more pronounced effect on regional fractional ventilation as a function of time.

Conclusion: Preliminary data suggests that regional fractional ventilation measurement using HP ^{3}He MRI can be used as a sensitive and noninvasive functional tool to assess the progression of emphysema at different stages of this pulmonary disorder. Longitudinal study of same subjects at different time points – as opposed to cohorts – will eliminate the expected intersubject variability and elucidate the sensitivity of this technique more explicitly.

References: [1] Z. Z. Spector, K. Emami, M. C. Fischer, J. Zhu, M. Ishii, V. Vahdat, J. Yu, S. Kadlecek, B. Driehuys, D. A. Lipson, W. Gefter, J. B. Shrager and R. R. Rizi, Magn. Reson. Med. 53 (2005), 1341-1346.