Imaging of Pulmonary Ventilation and Gas Exchange with Hyperpolarized ^{129}Xe in Mouse Models of Chronic Obstructive Pulmonary Disease Induced by Cigarette Smoke Solution and Lipopolysaccharide

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Introduction: Hyperpolarized (HP) ^{129}Xe MRI makes it possible to image the pulmonary airspace as well as tissues and blood in vivo with the information of lung structure and function, offering a powerful tool for the noninvasive assessment of the lung physiology in many types of animals from mice[1] to humans[2-4]. In this study we present HP ^{129}Xe MRI for quantitative assessment of ventilation and gas exchange with fully noninvasive manner in spontaneously breathing mice. To investigate the feasibility of this methodology for diagnosing the pulmonary disease, we applied this technique to a mouse model of chronic obstructive pulmonary disease (COPD) induced by multiple administration of cigarette smoke solution (CSS) combined with lipopolysaccharide (LPS).

Methods: 15 male ddY mice (6 weeks; 28-30 g) were randomized into two cohorts: sham instilled controls (N=8) and CSS+LPS-induced COPD models (N=7), which were prepared based on the method developed recently in guinea pigs[5]. Briefly, mice were intratracheally administered CSS (20 µl/instillation) once a day on days 0-3. Subsequently, an LPS solution (0.1 mg/ml, 20 µl/instillation) was administered on day 4, and then, mice were not received either CSS or LPS on days 5 and 6. This cycle was repeated 6 times for a period of 6 weeks, and then, MR measurements were performed. Mixed gas of 70%Xe(natural abundance)+30%N_2 was polarized at 0.15 atm using a home-built noble gas polarizer[6] and continuously supplied to mouth mask. Each mouse spontaneously breathed the gas after mixing with O_2. All MR measurements were performed at 9.4T (Varian Unity INOVA 400WB). Gas-phase ^{129}Xe was imaged by using a 2D multishot bSSFP sequence[7]. Acquisition parameters were: a 1000-µs Gaussian-shaped RF pulse with a bandwidth of 2800 Hz centered on the gas phase resonance, TR/TE=3.2/1.6 ms, acquisition bandwidth=62 kHz, matrix=64×32 (zero-filled to 128×64), FOV=8×2.56 cm^2, number of shot=4, NEX=8, flip angle=40°. Respiratory gated imaging for spontaneous breathing mice was performed by the protocol described previously[8]. For evaluating the ventilation, we modified the technique described earlier[9] for being applicable to the spontaneous breathing protocol. In brief, by varying the number of respiration (n) of HP ^{129}Xe+O_2 gas mixture from 1 to 10 before image acquisition, a series of ten ^{129}Xe images was obtained (Fig.1a). Each image was acquired at end-inspiratory phase. The ^{129}Xe signal build up in the lung was fitted by Eq.1 with pixel by pixel basis to yield the fractional ventilation r_a. Gas exchange was evaluated using XTC technique[10], in which two ^{129}Xe images of control and XTC were acquired at end-expiratory phase (Fig.1b)[8] for calculating the depolarization f_D as a quantitative measure of gas exchange, which is defined as the fraction of the gas phase signal that disappears as a result of the inversion of dissolved phase magnetization and subsequent exchange and calculated by Eq.2. For quantitative evaluation of the distribution of r_s and f_D within the lung, coefficient of variation (CV) was calculated from each map.

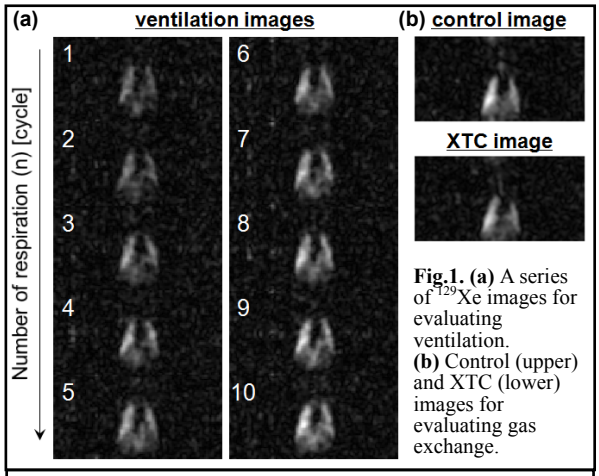

Fig.1. (a) A series of ^{129}Xe images for evaluating ventilation. **(b)** Control (upper) and XTC (lower) images for evaluating gas exchange.

$$M_a(n) = r_a M_f + (1-r_a) M_a(n-1)\exp(-\tau/T_a) = r_a M_f \left(\frac{1-((1-r_a)\exp(-\tau/T_{1a}))^n}{1-(1-r_a)\exp(-\tau/T_{1a})} \right) \quad [1]$$

$$f_D = 1 - \sqrt[n]{\frac{S_{XTC}}{S_{control}}} \quad [2]$$

M(n): ^{129}Xe magnetization in the lung after n breaths
M_f: fresh ^{129}Xe magnetization in the inhaled gas
τ: breathing cycle, T_{1a}: ^{129}Xe T_1 in the lung
$S_{control}$ and S_{XTC}: signal intensities of control and XTC images

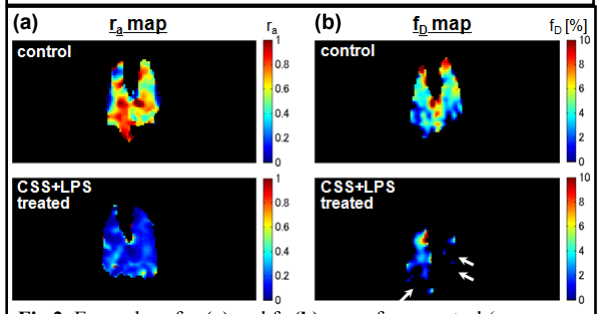

Fig.2. Examples of r_a **(a)** and f_D **(b)** maps from control (upper row) and CSS+LPS-treated (lower row) mice.

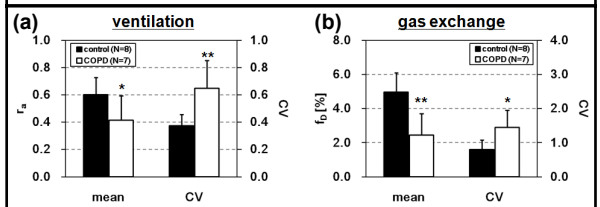

Fig.3. Comparison of lung functional parameters of r_a **(a)** and f_D **(b)** calculated from whole lungs between control and CSS+LPS-treated groups. *p<0.05 and **p<0.005.

Results and Discussion: Ventilation and gas exchange maps were successfully obtained from spontaneously breathing mice (Fig.2). Significant dysfunctions of ventilation and gas exchange in CSS+LPS-treated mouse were clearly shown from r_a (Fig.2a) and f_D maps (Fig.2b). For two groups of mice, lung functional parameters calculated from whole lungs were summarized in Fig.3. For all control mice, mean r_a value was 0.60±0.12 while was significantly reduced in CSS+LPS-treated mice to 0.42±0.18 (p=0.038). Significant enhancement of CV in CSS+LPS-treated mice (0.65±0.20) was observed when compared to control mice (0.37±0.08, p=0.004). The mean f_D value for control mice was 5.0±1.1 % while was significantly reduced in CSS+LPS-treated mice to 2.4±1.3 (p=0.002). CV of f_D showed the significant enhancement of CSS+LPS-trested mice; 1.5±0.5 for CSS+LPS-trested mice and 0.80±0.27 for control mice (p=0.009).

Conclusion: We demonstrated the feasibility of quantitative and regional assessment of ventilation and gas exchange with ^{129}Xe MRI in spontaneously breathing mice and found that this methodology is sensitive to differences in these pulmonary functions between the newly developed mouse models of COPD and controls.

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References: [1]Imai H, et al. ISMRM 2011, p880. [2]Cleveland ZI, et al. Plos One 2010;5:e12192. [3]Mugler JP, et al. PNAS 2010;107:21707. [4]Patz S, et al. New J Phys 2011;13:015009. [5]Mizutani N, et al. Biol Pharm Bull 2009;32:1559. [6]Imai H, et al. Concepts Magn Reson B 2008;33B:192. [7]Imai F, et al. Magn Reson Med Sci 2011;10:33. [8]Imai H, et al. NMR Biomed 2011, in press. [9]Deninger AJ, et al. MRM 2002;48:223. [10]Ruppert K, et al. MRM 2004;57:676.