Comprehensive Pulmonary Evaluation of Emphysematous Mice using Hyperpolarized ^{129}Xe MRI/MRS under Spontaneous Breathing Mode

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Introduction: Hyperpolarized (HP) noble gas MRI and MRS in the lungs on spontaneous breathing mice is expected as a valuable modality for drug discovery or development of the methods for evaluating physiological changes. Since the measurements under the spontaneous breathing condition are fully non-invasive protocol without using mechanical ventilation, this technique allows a long-term and the repeated measurements on the same individual. To evaluate pulmonary structures and functions comprehensively in diseased lungs is extremely important and that would be needed to measure at a nature respiratory state. In this work, we tried to detect changes of several important lung properties in a mouse model of emphysema by using HP ^{129}Xe MRI and MRS under the spontaneous breathing condition. Here the septal thickness and the volume ratio of the septum to the air space as pulmonary structures and ventilation, gas-exchange, and perfusion as pulmonary functions were evaluated in the same individual.

Methods: Seven male ddY mice (3 emphysema, 4 healthy) underwent a series of measurements described later. Emphysematous mice were prepared by endotracheal administration of elastase (300U/kgBW×2). Mixed gas of 70%Xe(natural abundance)+30%N_2 was polarized at 0.15atm using a home-built noble gas polarizer and continuously supplied to mouth mask [1]. Each mouse spontaneously breathed the gas after mixing with O_2. All MR measurements were performed with a Varian Unity INOVA 400WB high-resolution NMR spectrometer equipped with a 9.4T vertical magnet. Septal thickness, h, volume ratio, V_s/V_a, and mean transit time of blood through gas-exchange region, τ, were determined by CSSR described previously [2,3]. As a parameter for gas-exchange, depolarization of the gas-phase ^{129}Xe magnetization, f_d, was evaluated by XTC [4]. f_d was evaluated both at end-inspiratory and end-expiratory state (Fig.1a). To evaluate ventilation, two methods were used. First, a ventilation parameter, r defined as r=(1-S_{exp}/S_{insp})×100 was evaluated. Here S_{exp} and S_{insp} mean the signal intensity of the ^{129}Xe lung images at the end-expiration and end-inspiration, respectively (Fig.1a). Second, parameter MTT, which means the time constant of the recovery of gas-phase ^{129}Xe signal after the saturation, was evaluated by gas-phase ^{129}Xe saturation recovery (GPSR). For the HP ^{129}Xe gas imaging, bSSFP pulse sequence was used [2]. In the evaluation of f_d and r, bSSFP combined with CS technique was used for improving temporal resolution because fast acquisition were needed to acquire ^{129}Xe images at end-inspiratory and end-expiratory state under spontaneous breathing condition. By using the protocol, one image was able to acquire in 66ms with in plane resolution of 400×625μm^2. In the XTC measurements, four inversion pulses were repetitively applied with a delay time of 20ms for labeling the dissolved-phase magnetization before gas-phase ^{129}Xe imaging. GPSR was performed as follows. Total of eleven gas-phase ^{129}Xe images were acquired by bSSFP following a saturation pulse centered at 0ppm (gas phase) with 11 delay times (Δt) in between 0.002 and 5s (Fig.1b). Images were acquired with NEX=8 for each delay time. MTT was calculated for pixel by pixel from these images by least squares fitting with $S(\Delta t) = S_0(1\text{-}\exp(-\Delta t/\mathrm{MTT}))$.

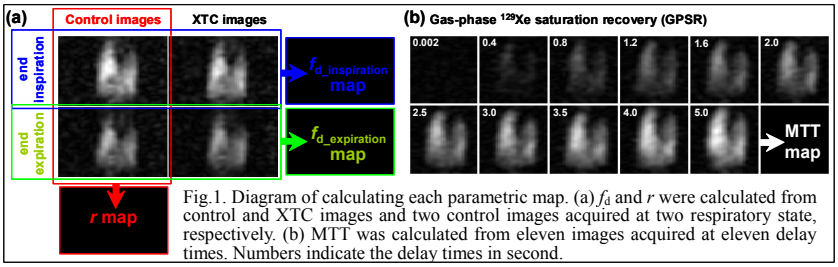

Fig.1. Diagram of calculating each parametric map. (a) f_d and r were calculated from control and XTC images and two control images acquired at two respiratory state, respectively. (b) MTT was calculated from eleven images acquired at eleven delay times. Numbers indicate the delay times in second.

Results and Discussion: From the results of CSSR measurements (Fig.2a), it is found that the volume ratio V_s/V_a was significantly reduced in emphysematous mice reflecting the destruction of alveolar wall. Also, the septal thickness, h, and transit time of blood, τ, were significantly increased in emphysematous mice (Fig.2c). This tendency differs from our previous study [3]. From the imaging studies, significant differences were found for both ventilation parameters, r and MTT, reflecting the ventilation defects (Fig.2c). The region of ventilation defect was clearly found in r map as well as MTT map (Fig.2b). On the other hand, significant difference was not shown for f_d in both respiratory state (Fig.2c). Although declining trend of f_d in whole lung and local reduction in f_d maps (Fig.2b) were shown in emphysematous mice, further improvement of this method is needed for application to spontaneous breathing mice. Hitherto HP ^{3}He MRI on spontaneously breathing animals have been reported, wherein the ventilation was evaluated [5]. On this contrary, our study showed that inherent advantage of HP ^{129}Xe such as high solubility in tissue and blood as well as large chemical shift distribution allows detection of several important parameters related to lung structure and function in addition to ventilation.

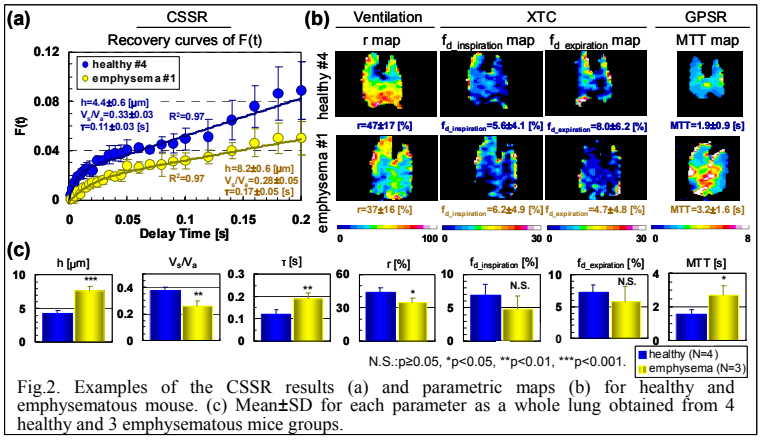

Fig.2. Examples of the CSSR results (a) and parametric maps (b) for healthy and emphysematous mouse. (c) Mean±SD for each parameter as a whole lung obtained from 4 healthy and 3 emphysematous mice groups.

Conclusion: By applying the several techniques for evaluation of pulmonary structure and function, abnormalities were successfully detected in emphysematous mice in the structure, perfusion and ventilation. It was shown that the method described here could become useful for drug research and development using small rodents since this protocol was able to detect pathological changes non-invasively.

References: [1] H. Imai, et al. ISMRM 2009;17:2209. [2] S. Patz, et al. ISMRM 2008;16:2678. [3] H. Imai, et al. ISMRM 2009;17:2212. [4] K. Ruppert, et al. Magn Reson Med 2004;51:676. [5] V. Stupar, et al. NMR Biomed 2007;20:104.