Quantitative Assessment of Emphysema with Dissolved-Phase and Gas-phase Hyperpolarized ^{129}Xe MRI in Mice

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Introduction: A unique aspect of hyperpolarized (HP) ^{129}Xe, the high solubility of Xe in blood and tissues and its large chemical shift distribution, is attractive for pulmonary MRI. Recently, direct imaging of dissolved-phase (DP) ^{129}Xe in the lung has been possible in addition to the gas-phase (GP) imaging[1-4]. It is expected that the method provides new opportunities to comprehensively evaluate the regional physiological changes of the diseased lungs. In our previous study with HP ^{129}Xe lung MR, it has been proven that a chemical shift saturation recovery (CSSR) method[5] is effective for assessing emphysema in spontaneously breathing mice[6]. We experimentally observed the fraction F(t), which is the ratio of ^{129}Xe magnetization in the septa at recovery time t relative to that of the gas space at t=0, reduced in the elastase-treated mouse models of emphysema throughout the recovery time, reflecting the alveolar tissue destruction. From the aspect of this whole lung study, we hypothesize that the alveolar destruction can be regionally and quantitatively evaluated by F map created by the combination of GP and DP ^{129}Xe images. In this study we investigate the feasibility of quantitative assessment of emphysema using F map in spontaneously breathing mice.

Methods: 10 male ddY mice (6 weeks; 28-30 g) were randomized into two cohorts: sham instilled controls (N=5) and elastase-induced emphysema (300U/kgBW, N=5). MR measurements were performed at 2 weeks after the elastase administration. Mixed gas of 70%Xe(natural abundance)+30%N_2 was polarized at 0.15 atm using a home-built noble gas polarizer and continuously supplied to mouth mask[7]. Each mouse spontaneously breathed the gas after mixing with O_2. All MR measurements were performed at 9.4T (Varian Unity INOVA 400WB). GP and DP ^{129}Xe were imaged by using a non-slice selective 2D ultrashort TE (UTE) sequence to overcome its short T_2^*. Acquisition parameters were: 200 radial views, 32 sampling points, matrix=64×64 (zero-filled to 128×128), FOV=4×4 cm^2, TE=0.2 ms. DP image was acquired with NEX=64, TR=50 ms, and flip angle (α) =90°. For GP imaging, 4 views per 1 segment were acquired by using a variable-flip-angle method[8] with TR=5 ms and NEX=1, and each segment was separated by 5-sec interval so that the depolarized ^{129}Xe gas was fully replaced with fresh HP gas by spontaneous breathing. GP (0ppm) and DP (197ppm) ^{129}Xe were selectively excited with a 0.3 ms-Gaussian-shaped pulse, which provides completely selective excitation with the aid of the large difference in frequency between GP and DP signals (~20 kHz at 9.4T). F was calculated from GP and DP images according to Eq.1 with pixel by pixel basis. Where, M is the magnetization and s is the signal intensity of ^{129}Xe image. T_2^* for each phase was evaluated as a single value from whole lung using the relation $T_2^*=1/(\pi\mathrm{FWHM})$, where FWHM was estimated by fitting of the ^{129}Xe spectra at 50-ms delay in CSSR to Lorentzian shape[9]. DP ^{129}Xe image acquisition with 90° flip angle and TR=50 ms gives F meaning as the relative amount of DP magnetization of ^{129}Xe diffused into septa within 50 ms[1]. For quantitative evaluation of the distribution of F within the lung, coefficient of variation (CV) was calculated from F maps. For investigating the relationship between the parameters assessed from HP ^{129}Xe MRI and alveolar destruction, surface-to-volume ratio (S/V) was histologically evaluated and it was compared to mean F and CV values.

$$F=\frac{M_{DP}}{M_{GP}}=\frac{s_{DP}}{s_{GP}}\cdot\frac{NEX_{GP}}{NEX_{DP}}\cdot\frac{\exp\left(-TE/T_{2GP}^*\right)}{\exp\left(-TE/T_{2DP}^*\right)}\cdot\frac{\sin\alpha_{GP}}{\sin\alpha_{DP}} \quad [1]$$

Results and Discussion: GP and DP ^{129}Xe images were successfully acquired from spontaneously breathing mice with the aid of UTE sequence (Fig.1). Low signal intensity of the DP image in elastase-treated mouse was observed. In control mice, higher F values were seen throughout the lung with relatively homogeneous distribution, whereas the elastase-treated mice exhibited the low F values with a greater heterogeneity within the lung (Fig.2a). For all control mice, mean F value was 3.4±0.5 % while was significantly reduced in elastase-treated mice to 2.3±0.5 % ($p<0.006$). Significant enhancement of CV in elastase-treated mice (0.43±0.04) was observed when compared to control mice (0.23±0.01, $p<10^{-5}$). The lower F values in the elastase-treated mice indicated alveolar destruction, which was confirmed from histologically derived S/V; 881±136 cm^{-1} and 374±102 cm^{-1} for control and elastase-treated mice, respectively ($p<0.0005$). The mean F value and CV had significant correlation with S/V (Fig.2b). For more precise determination of regional F value, regional information regarding T_2^* is needed because T_2^* in both GP and DP change reflecting the lung microstructure[10,11]. In fact, the term of T_2^* in Eq.1 ($\exp(-TE/T_{2\,GP}^*)/\exp(-TE/T_{2\,DP}^*)$) showed the significant difference between two groups; 1.62±0.04 for control and 1.82±0.11 for elastase-treated mice ($p<0.02$).

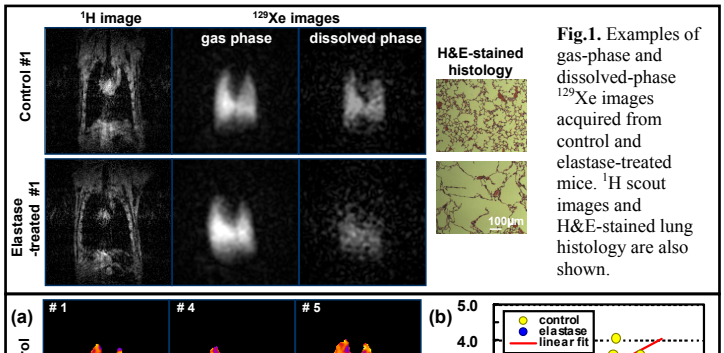

Fig.1. Examples of gas-phase and dissolved-phase ^{129}Xe images acquired from control and elastase-treated mice. ^{1}H scout images and H&E-stained lung histology are also shown.

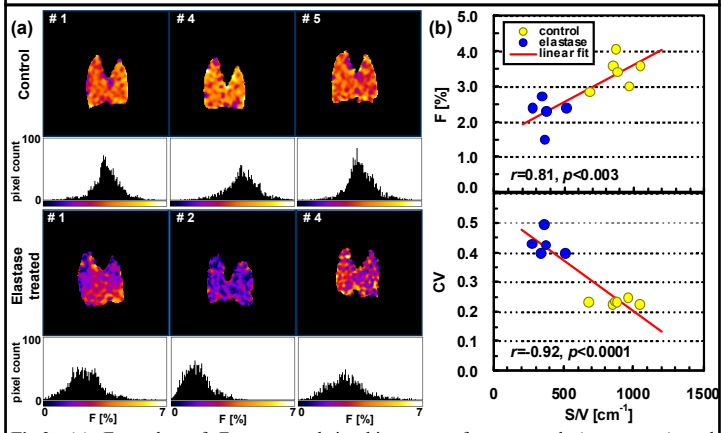

Fig.2. **(a)** Examples of F maps and its histograms from control (upper row) and elastase-treated (lower row) mice. **(b)** Correlation between S/V derived from histology and mean F and CV values assessed from HP ^{129}Xe MRI.

Conclusion: We demonstrated the feasibility of quantitative assessment of regional alveolar tissue destruction with a combination of GP and DP ^{129}Xe MRI in spontaneously breathing mice and this work suggests that this fully noninvasive method provides longitudinal evaluation of the pulmonary diseases in small rodents under a nature respiratory state.

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