

LUNG FUNCTION ASSESSMENT IN A MOUSE MODEL OF EMPHYSEMA USING ULTRASHORT ECHO-TIME AND OXYGEN-ENHANCED MRI

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Purpose: Emphysema is one of the hallmarks of chronic obstructive pulmonary disease (COPD) and is characterized by enlargement of air spaces caused by destruction of the alveolar walls. Tissue damage leads to 1) increased air volume relative to tissue mass, and 2) impairment of oxygen transfer from the alveolar space to the blood circulation. Tissue loss in emphysema has been shown to affect the MRI signal intensity (1) and oxygen-enhanced MRI (OE-MRI) has been applied to detect regional ventilation deficits and alveolar-capillary gas transfer impairment of molecular oxygen in COPD patients (2). The aim of this study was to utilize OE-MRI to assess pulmonary function in an experimental model of COPD induced in mice.

Methods: In vivo experiments were approved by the local animal research ethics committee. Female C57 mice (n=20) were anaesthetized and 6.25U/ml of Porcine Pancreatic Elastase (PPE) (n=10) or vehicle (saline) (n=10) were instilled intranasally (i.n) at days 0 and 7. MR imaging was performed on free-breathing mice at 4.7 Tesla (Bruker BioSpec) 12 days after the second PPE challenge. A series of axial T1-weighted images were acquired using a segmented inversion-recovery 2D-UTE sequence (400 radials/image, intra-segment time TS=3.4ms, TE=0.5ms, number of segments=10, steps per segment=40, FOV=40mm, slice thickness=1.6mm, FA=12°, NA=2, TA=2.1 min) (3). T1 values were 100, 400, 700, 1800, 3000, 4500 and 6000ms. A fat suppression module was used prior to each segment to reduce the contribution from short T1 components. Acquisitions were performed while breathing first air and then 100% oxygen. A three-parameter fitting algorithm was applied to estimate T1 and proton density (PD) on a pixel level. A two-tailed t-test was applied for statistical analysis. After the experiment, the animals were euthanized and their lungs sectioned for histological observation. A separate group of vehicle (n=5) and PPE (n=5) mice was used to access lung mechanical properties using a flexiVent-system (FScireq, Montreal, QC, Canada).

Results: Histology results revealed a moderate to marked loss of tissue connectivity and mild perivascular lymphocytic inflammation in PPE mice. A significant increase (p<0.05) in compliance and mean delivered volume was measured in PPE mice with flexiVent. All animals were successfully imaged in a 30 min session. UTE MRI showed the effect of PPE in images and corresponding PD and T1 maps (Fig1). MRI proton density in the lungs of PPE-treated mice was 11% lower than control mice (p<0.001) (Fig 2a). Lung T1 (mean ± SEM over 10 animals) was 1850±10ms for vehicle and 1865±18ms for PPE-treated animals breathing air (Fig 2b). Significant T1 shortening due to oxygen was seen in each group (4.5% in control vs 5% in PPE, p<0.001), however there were no differences in mean lung T1 change over the whole lung observed between the groups (Fig 2c,d). The mean T1 in back muscle was 1696±12ms and 1690±12ms for saline and PPE groups, respectively. Muscle T1 in the vehicle group did not change after oxygen inhalation, but muscle T1 shortened by 2 % in the PPE-treated group (p=0.01).

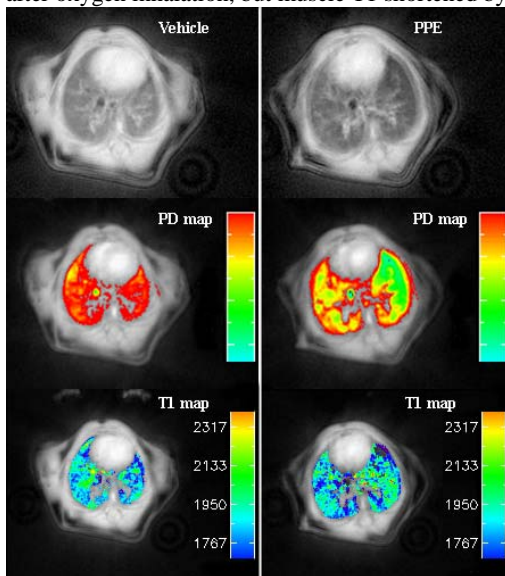


Fig.1 Typical UTE images with corresponding proton density and T1 maps for a vehicle and a PPE-treated mouse.

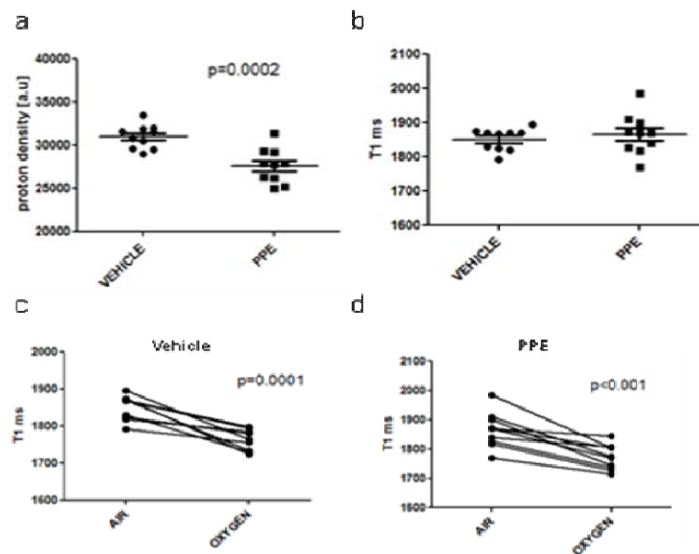


Fig. 2. Lung MRI proton density (a) and T1 (b). Change in lung T1 in vehicle (c) and i.n. PPE-treated (6.25U/ml) mice (d).

Discussion and conclusions: To our knowledge this is the first study where UTE has been used to measure oxygen enhancement in a mouse model of COPD. Alveolar connectivity loss and loss of elasticity in PPE mice indicated that repeated intranasal instillation of PPE induced emphysema. UTE MRI detected decreased proton density reflecting the destruction of lung parenchyma. However, no difference in global oxygen enhancement between the groups was found. In this COPD model it is possible that healthy well ventilated regions compensate for loss of function in damaged areas and/or that oxygen is dissolved in fluids associated with an inflammatory response. Further investigation to understand the heterogeneity of tissue response to oxygen inhalation is underway. The imaging protocol is easy to implement, less than 30 min duration per animal, does not require mechanical ventilation, and is appropriate for longitudinal investigations. This MRI protocol is well suited for routine drug testing in experimental MR lung research of COPD.

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References: 1. Quintana et al. MRM 56:1242-1250 (2006) 2. Ohno et al. AJR 190 (2008), 3. Zurek et al. Proc. Intl. Soc. Mag. Reson. Med. 20 (2012).