Longitudinal and non-invasive assessment of emphysema evolution in a murine model using proton MRI

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Purpose: Emphysema is characterized by an enlargement of airspaces caused by destruction of the alveolar walls. Subsequent tissue density losses and microstructural changes of the lung parenchyma have been shown to affect both, the MR image intensity and T_2* values in several animal models of emphysema disease (1-3). The aim of this study was to investigate the potential of the ultra-short echo-time (UTE) proton MRI technique to track emphysema disease progression along an 8-weeks longitudinal study in elastase-challenged mice. MRI findings were compared with histomorphological measurement endpoints.

Methods: Male C57 mice (n=16) were anaesthetized and 50 µL/kg of Porcine Pancreatic Elastase (PPE) (n=9) or saline (n=7) were administered into the surgically exposed trachea. MR imaging was performed at 4.7 Tesla prior to instillation, 24h, 3 weeks and 8 weeks after PPE challenge. A set of axial images was acquired using a multislice radial UTE sequence (400 radials/image, TR=80ms, flip angle=20deg, slice thickness=1.7 mm, number of slice=6, number of averages=8). To assess T_2* values, images with five TE values (0.55, 0.97, 1.26, 1.76, 2.46 ms) were acquired. The scan time needed to acquire proton density-weighted images and T_2* maps was about 21 minutes for each animal. At 8 weeks, animals were euthanized and their lungs sectioned for histological observation.

Results: Histology results revealed more prominent alveolar expansion in the left lungs compared to the right lungs (observation presumably due to the instillation protocol). Concerning MR results, the effect of elastase on the lung can be seen from axial proton images as the expansion of the lung volume through the experimental protocol (Fig. 1). The normalized MR mean signal intensities (at TE equal to 0.55 ms) in the left lung measured 3 and 8 weeks after challenge were significantly lower (p=0.01, t-test) in the animals treated with PPE, compared to their baseline (Fig. 2 left). The decline of the MR mean signal intensity measured 8 weeks after the challenge was equal to 30%. In accordance with the histology findings, this observation was less prominent in the right lung (p>0.05). A large (30% decrease) and significant (p=0.04 at 8 week) T_2* shortening was observed in the left lung (Fig 2, right), while no specific T_2* behavior was found in the right lung.

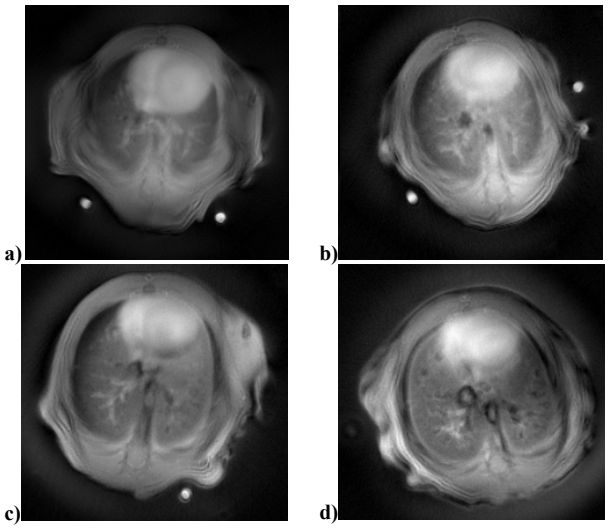

Fig. 1: Images of mouse thorax from the same animal acquired prior to (a) and 24 h (b) as well as 3 (c) and 8 weeks (d) following the PPE challenge.

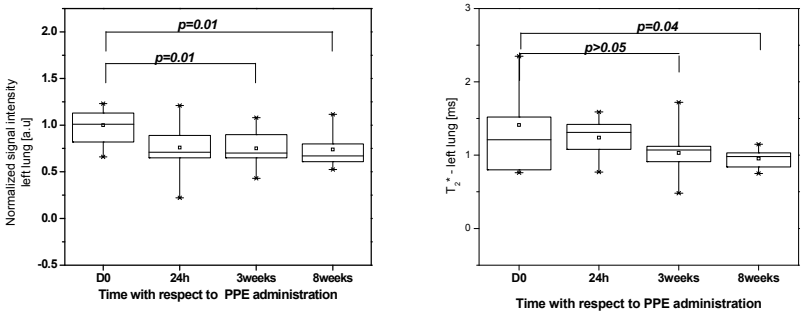

Fig.2: Signal intensities (left) and T_2* kinetics (right) measured from the left lung parenchyma with regards to time after administration of PPE. The bottom and top of the box are the lower and upper quartiles, respectively; the band near the middle of the box is the median; the ends of the whiskers represent the minimum and maximum of all the data; the open squares represent the mean.

Discussion and conclusions: At a very short echo time, the drop of the mean signal intensity measured during the disease progression reflects the decrease of spin density in emphysematous lung. This signal intensity decline is in a good agreement with tissue density losses reported in studies performed with similar experimental conditions (4). According to a physical model of magnetic field perturbers in a tissue matrix (5), the T_2* values are expected to scale with the tissue density in the lung parenchyma. Indeed, the observed amplitude of T_2* changes was similar to the amplitude of image intensity changes (30% decrease at 8-weeks). In conclusion, the UTE technique allows the detection of signal intensity and T_2* changes in the lungs caused by progression of emphysema disease. The imaging protocol is easy to implement, does not require intubation or mechanical ventilation, and is appropriate for longitudinal investigations. This technique is readily suitable for routine drug testing in experimental MR lung research of emphysema and can be transferred to human studies.

References: 1. Quintana et al. MRM 56:1242-1250 (2006) 2. Olsson, et al. JMRI 25: 488-494 (2007), 3. Takahashi et al. JMRI 32: 326-333 (2010) 4. Postnov et al. J. Microsc 220:70–75 (2005) 5. Yablonskiy et al. MRM 32:749–63 (1994).