SIMILAR T1 CHANGES ARE FOUND IN A TRANSLATIONAL STUDY IN THE LUNGS OF HUMAN SMOKERS AND MICE EXPOSED TO TOBACCO SMOKE

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Introduction: Cigarette smoking is the leading cause of chronic obstructive pulmonary disease (COPD). An ultra-short echo time (uTE) sequence has recently been used to image the lungs of small animals [1]. In this study, a murine model of acute exposure to tobacco smoke (TS) is utilized to determine pulmonary signal intensity (SI) on T_1-weighted uTE images. The findings are compared with the results of a human study, which used the Look-Locker method [2,3] to estimate T_1 in the lungs of a group of non-smoking and smoking volunteers.

Methods: ***Preclinical*** The study was approved by the local ethics review board for animal studies. Lung MRI uTE 3D acquisitions on a small group of spontaneously breathing female C57B1/6J mice (9-10 weeks old) were performed using a 9.4 T MRI scanner (Bruker Biospec 94/20, Ettlingen, Germany). T_1 estimation was performed on 3 animal groups (n=3/group): 1 control group (air exposed) and 2 TS groups (exposed to cigarette smoke for 18 days). The second TS group was exposed to TS in combination with Polyinosinic-Polycytidylic acid (pIC), synthetic analog of double stranded RNA, which induces accelerated emphysema and fibrosis [4]. The imaging parameters were: TR=10 ms, TE=20 µs, FA=4° and 20°, FOV=30^3 mm^3, matrix=96^3 and NA=1 with a total acquisition time of approximately 20 min. Signal analysis in lung was performed by placing 4 equally sized circular regions of interest (ROIs) on each slice and one customized region in muscle tissue on 7 central axial lung slices. Bronchoalveolar lavage (BAL) fluid analysis was carried out to study the pulmonary inflammation on the TS exposed animals.
Clinical Informed consent was taken from 23 volunteers (10 males and 13 females, aged 23-57), 11 of whom were current non-smokers, and the remaining 12 current smokers. Smokers with a range of pack-years (PY) from 1.6 to 40 PY (number of years or equivalent years in which 20 cigarettes a day was smoked) were included. Heavy smokers (subset of the smokers group) were defined as having >20 PY (5 subjects). A snapshot FLASH acquisition with RF spoiling [2] was carried out on a 1.5 T Philips Achieva system (Philips Medical Systems, Best, NL). The imaging parameters were: TR=2.2 ms, TE=1.0 ms, FA=5°, FOV=445^2 mm^2, slice thickness=15 mm, matrix=128x256 (zero filled to 256x256) and NA=10. Images were registered using techniques defined in [3] to remove respiratory motion and T_1 was obtained by fitting the Look-Locker equation [5] pixel-by-pixel for the single slice. Median T_1 values were calculated for each subject for a whole slice ROI.

Results: Figure 1 shows significant normalised lung SI increases for the preclinical TS and TS pIC groups in comparison with the control group on T_1-weighted images (FA = 20°). No significant differences in lung SI were found with a FA = 4° and no significant changes were observed in muscle with the two FAs. Lung T_1 was lower in TS animals than in the control animals (Figure 2). The total number of leukocytes in BAL fluid was significantly increased in TS animals compared to control animals ($p \leq 0.001$). Figure 3 shows the same trend in the clinical study, revealing a significant decrease in T_1 in smokers and a further decrease in heavy smokers.

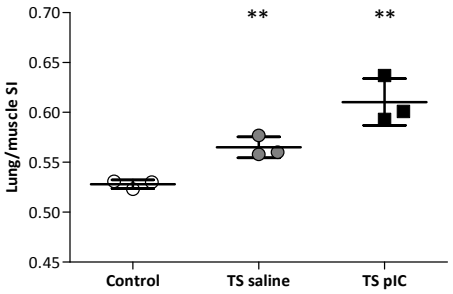

Figure 1. Mean normalized lung SIs at T_1-weighted acquisitions (FA=20°) for control, TS saline and TS pIC animals. $^{**}p < 0.01$ by Student's t-test.

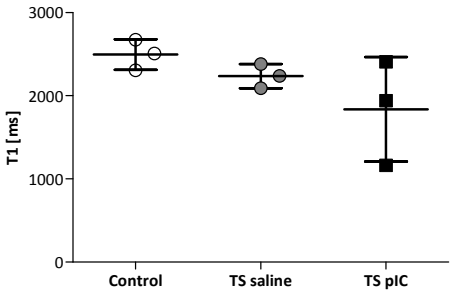

Figure 2. Estimated lung T_1 relaxation times for control, TS saline and TS pIC mice.

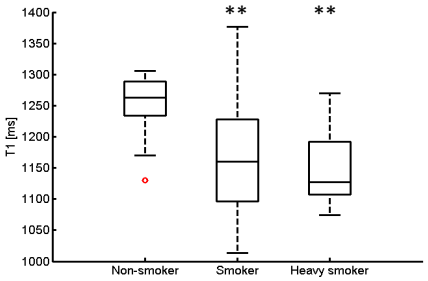

Figure 3. Estimated lung T_1 relaxation times from Look-Locker sequences for non-smokers, smokers and heavy smokers (>20 pack years). $^{**}p < 0.01$ by Student's t-test.

Discussion and Conclusion: Significant lung SI increases on T_1-weighted images were found in the preclinical groups exposed to TS. T_1 was decreased for TS animals, which is not only compatible with the findings of the smoke exposure in humans shown here (Figure 3), but also with data demonstrating a T_1 decrease in COPD, emphysematous and fibrosis lungs [6,7,8]. The changes in T_1 were not significant (Figure 2), possibly due to the small animal numbers, however a trend remained. Histological changes with induced accelerated emphysema and airway fibrosis in TS animals have been observed in other experiments. A translational link between humans and animals exposed to TS expressed as decreased T_1 has been demonstrated. Further work, using a larger sample size, is required to explain the TS lung SI changes and to explore the potential of using MRI in these TS induced models of COPD in the future.

References: [1] Togao O *et al*. JMRI 2011;34:539-546. [2] Jakob PM *et al*. JMRI 2001;14:795-799. [3] Naish JH *et al*. MRM 2005;54:464–469. [4] Kang MJ *et al*. JCI 2008;118(8):2771–2784. [5] Deichmann R and Haase A. JMRI 1992;96:608-612. [6] Hubbard P L *et al*. Proc. ISMRM 2011;19:542. [7] Stadler A *et al*. MRM 2008;59:96-101. [8] Stadler A *et al*. JMRI 2005;21:759-764.