Non-invasive assessment of mucociliary clearance with micron-sized iron oxide particles in rat lungs

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death and one of the few major diseases associated with rising mortality rates [1]. It is characterized by airflow limitation, chronic inflammation of the respiratory tract and frequently excess mucus production. The clearance of mucus from the bronchial airway surfaces is an important protective mechanism for the removal of bacteria and noxious substances. A critical role in the efficient clearance of mucus is played by the fluid layer – the "airway surface liquid (ASL)". The volume and viscosity of the ASL is regulated by the flow of water between the epithelial cells and the surface layer. In the diseased lung various factors contribute to an imbalance in the amount of ASL. Pathologic changes resulting from exposure to cigarette smoke or other toxic agents increase the production of mucin. The reduction in mechanical clearance of mucus from the diseased lung may trigger exacerbations in COPD by repeated and prolonged periods of infection or even chronic bacterial colonization of mucus adherent to airway surfaces [2]. New therapeutic approaches aim at the improvement of mucociliary clearance (MCC) in these patients. To allow measurement and monitoring of MCC in patients the development of a non-invasive technology which detects also small changes in MCC is required. Using MR as imaging technology, the very short T_2 and T_{2^*} relaxation times in the lung requires the utilization of MR imaging sequences providing very short echo times to visualize lung parenchyma. In this study we used 2D radial FID sampling techniques with a Gaussian-shaped RF excitation. The aim of the present study was to evaluate MCC through application of micron-sized iron oxide particles in the lung of rats.

Methods

Four different micron-sized iron oxide particles with diameters of, 2.8 µm, 4.5 µm or 10 µm, were used. The 2.8 µm particles were coated either with amine- or carboxyl-groups (Invitrogen Dynal AS, Oslo, Norway). The 4.5 µm (Invitrogen Dynal AS, Oslo, Norway) and the 10 µm particles (Bangs Laboratories, Fishers, USA) were uncoated. Prior to application particles were suspended in 0.5% Natrosol solution. Two dosages of these particles (0.25 and 0.5 mg) were applied into the left lobe of the lung by intratracheal instillation under isoflurane anaesthesia. MRI was performed using a Bruker Biospec 47/40 scanner (Bruker BioSpin, Ettlingen, Germany). For rat lung imaging, a 2D radial gradient echo with FID sampling was implemented [3]. After a conventional slice excitation, the slice refocusing gradient is realized with maximum slew rate of the gradient system in order to achieve minimum TE. With a Gaussian RF excitation pulse of 300 µs a minimum TE of 500 µs was achieved. Further parameters were: five slices, flip angle $\alpha = 15°$, slice thickness = 3.2 mm, FOV = 6 cm, in-plane resolution of 234 µm. The experiment was triggered by the respiration signal of the animal. Image reconstruction included a phase-correction of every projection based on the k = 0 sample, 1D gridding of the ramp-sampled points followed by the filtered backprojection using the Ram-Lak filter function [4]. MRI was performed at day 0, 1 and 2 after application.

Results

Application of 0.5 mg of the four different iron oxide particles maintained an attenuation of MR signal intensity in the rat lung at day 0 after measurement (example shown for the 4.5 µm particles, Fig. 1a). MR measurements 1 and 2 days after application did not reveal a full recovery of signal intensity in the lung for any particle (Fig. 1b, 1c). Intratracheal instillation of half the dose (0.25 mg) exhibited a clearance from the lung within one day in the case of the 4.5 µm sized particles (Fig. 2), whereas the 2.8 µm- and 10 µm-sized iron oxide particles at the doses of 0.25 mg were not cleared form the lung within one day.

Conclusions

Our results indicate the great advantage of using 2D radial FID sampling techniques to visualize even fine structures in the rat lung. The application of micron-sized iron oxide particles into the lung caused an attenuation of signal intensity, which fully recovered within one day in the case of application of 0.25 mg of the 4.5 µm sized particles, indicating that these particles may be suitable to visualize and quantify mucociliary clearance also in patients.

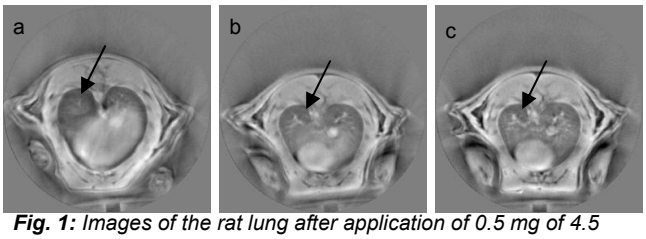

Fig. 1: *Images of the rat lung after application of 0.5 mg of 4.5 µm-sized particles. (a) Day 0, (b) Day 1 after application, (c) Day 2 after application.*

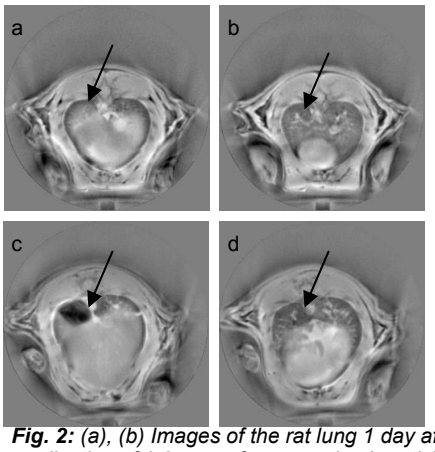

Fig. 2: *(a), (b) Images of the rat lung 1 day after application of 0.25 mg of 4.5 µm-sized particles. (c), (d) Images of the rat lung 1 day after application of 0.5 mg of 4.5 µm-sized particles.*

References

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