In vivo 3D mapping of aerosol deposition in rat lungs

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Introduction

Inhalation therapy has broadened its field of application over the last two decades by considering the lung as a portal to access systemic circulation. Systemic delivery across the oronasal route is investigated for a number of indications including migraine, diabetes, pain, and cancer[1]. This approach was made possible by the emergence of biotherapeutics and a greater understanding of the absorption properties of the lung[2]. However, progress into the market of systemic aerosolized drug delivery has been slowed down to-date by a number of confounding factors including rapid clearance, instability, longterm toxicity, and dosing issues[3]. Final drug distribution in such a complex system as the lung strongly depends on a variety of parameters like the aerosol administration protocol, particle size, density, and physicochemical properties, as well as the airway geometry. Independently of drug formulation and pharmacokinetic considerations, these parameters determine the deposition distribution throughout the lung. Quantification and spatial localization are of critical importance to better control and optimize drug concentration at specific or less- and nonspecific sites. Nuclear medicine techniques are currently the only available modalities that combine both aerosol quantification and regional localization. They are considered as reference techniques even though they remain limited by their spatial and temporal resolution as well as by patient exposure to radiation. With regard to lung imaging, hyperpolarized helium-3 MRI has been developed as a powerful tool to quantitatively characterize the parenchyma and the organ function and morphology[4,5]. The technique is innocuous and provides millimeter and sub-second resolution with high signal to noise ratios. We present here a new imaging modality utilizing hyperpolarized helium-3 MRI to probe superparamagnetic iron oxide (SPIO) labeled aerosols. This method uses hyperpolarized helium-3 phase-shifts resulting from the strong dipolar field in the region of SPIO particles deposition to visualize the aerosol deposition in rat airways.

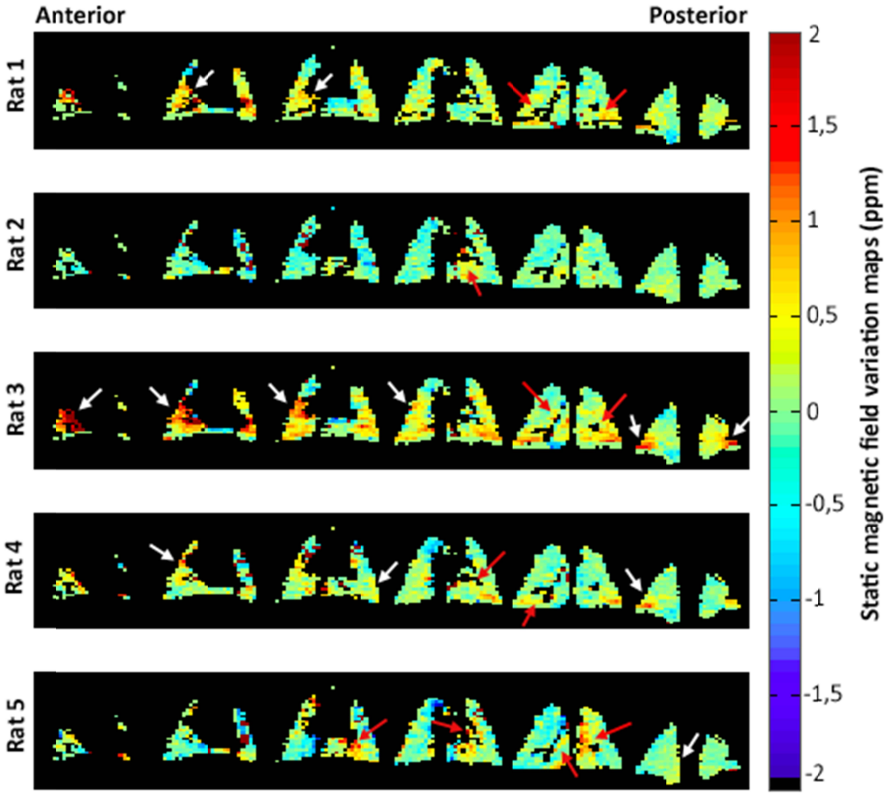

Figure 1: Static magnetic field maps B_{FE} (in ppm) calculated from subtracted phase maps acquired before and after aerosol administration after spatial normalization. The images are presented in the coronal plane for 5 rats.

Material and methods

Experiments were carried out *in vivo* on 5 anesthetized and tracheotomized healthy male Wistar rats. A catheter was inserted in the trachea and connected to a custom-built gas administration platform. The gas administration platform was used to ventilate the animal, monitor the pressure at the animal mouth, set and launch hyperpolarized helium-3 administration sequences. The animal ventilation rate was set to 60 breaths/min with a maximum inflation pressure set to 10 mbar. The MR labeled aerosol was obtained by dilution of a superparamagnetic contrast agent (Cliavist®, Bayer Schering Pharma, Germany) into isotonic saline to reach an iron concentration of [Fe] = 10 $g \cdot L^{-1}$, then nebulized with an ultrasonic device (Aeroneb® Solo, Aerogen, Republic of Ireland) during 10 min. Hyperpolarized helium-3 MRI was performed at 1.5 T (Achieva®, Philips Medical Systems, The Netherlands) using a 3D gradient-echo sequence during a single breath hold. The parameters were as follow: matrix=64×32×22, FOV=80×40×27.5 mm, TE/TR=5/11 ms, α=3.6°. Total MR scan time was 7.7 s. For each rat, two sets of images were acquired, before and after administration of the labeled aerosol. The images were spatially normalized and the phase maps were extracted.

The phase maps acquired before aerosol administration were subtracted from those acquired after aerosol deposition and from these the static magnetic field B_{Fe} was computed.

Results

Figure 1 shows the static magnetic field maps B_{Fe} resulting from the deposition of iron labeled aerosols *in vivo*, in 5 rat lungs. Important perturbations are measured at the two main bronchi periphery (red arrows) while the highest variations occur in the anterior part of the lung (white arrows).

Conclusion

Static magnetic field variation maps B_{Fe} could be calculated thus revealing the regional distribution of an MR labeled aerosol, *in vivo*, in 5 rats. As expected, major deposition occur at the first bronchi generations, mainly resulting from impaction phenomenon. The use of a custom built gas administration platform provided high reproducibility. Spatial normalization of the acquired images allowed us to characterize the reproducibility of the administration setup while eliminating discrepancies that may result from inter subject morphological differences.

Reference

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