Manganese: a new contrast agent for lung imaging?

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Purpose: MR imaging of lungs presents a particular challenge, due to weak MRI signals obtained (1). The use of T1-shortening contrast agents such as gadolinium chelates can improve the anatomic resolution of pulmonary imaging (2). Gadolinium-based aerosols, however, are viscous, and the signal enhancement in the lung increases with decreasing viscosity of the contrast agents (3). The viscosity problem can be overcome by using other T1-shortening contrast agent, e.g. manganese. A particular advantage of manganese is its small size, compared to macromolecular gadolinium-based contrast agents (e.g. Gd-DTPA), which make it more suitable for pharmacological applications. The aim of this study, therefore, was to evaluate the usefulness of manganese (MEMRI) for animal lung imaging.

Materials and Methods: MRI images were acquired at 4.7 T with a radial UTE sequence (400projections/128 points, TE/TR=0.55/29 ms, FOV=60mm, slice thickness=1.7 mm, number of slice=6, number of averages=10). To optimize the T1-enhancement, the images were acquired with four different values of flip angle equal to 15°, 30°, 45° and 60°. Sprague Dawley rats (400±50g) were anaesthetized with an intra-peritoneal injection of a mixture containing ketamine and medetomidine. A sterile cannula was introduced orotracheally to one of the main bronchi and held in place for subsequent instillation of the compounds. A baseline MRI was first acquired. Then, a second scan was performed, after the administration of either 200µl of manganese chloride hydrate solution ($MnCl_2$, x H_2O) or saline, without changing the position of the animal within the magnet. Four concentrations of $MnCl_2$ were investigated, (0.01, 0.1, 1 and 10 mM). Post scanning, the rats were sacrificed and the position of the catheter in the lung was verified. The Mn^{2+} related signal enhancement was evaluated on six axial MRI slices covering the lung volume. The intensity of the signal in a given ROI was divided by the intensity of the signal in the non-injected lung for normalization. Signal enhancement was defined as the relative change in normalized signal intensity pre and post $MnCl_2$ instillation.

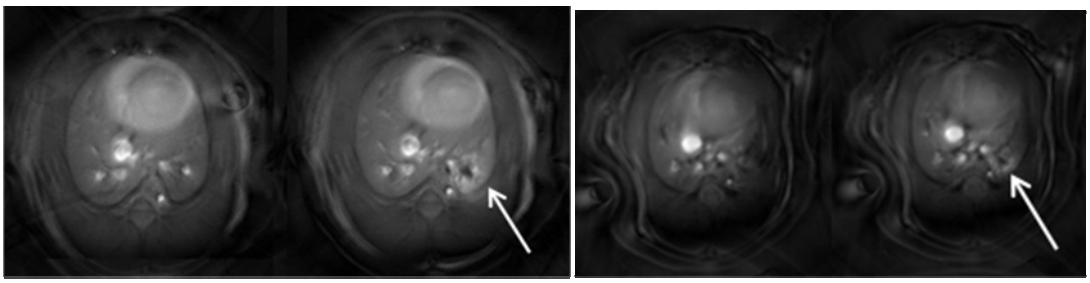

Fig.1 The pair of images on the left is representative for $MnCl_2$ solution (1 mM). The images on the right were obtained for a 10 mM $MnCl_2$ solution. The flip angle was equal to 60° for both data sets. The arrows indicate enhanced regions in left lungs following instillation.

Results: The signal enhancement (SE) corresponding to saline instillation was constant through the different flip angles (FA) and equal to 6% when averaged over all the axial slices. Following instillation of $MnCl_2$ solution, image intensity changes were appreciable for concentration of 1 and 10 mM in the left lung (Fig.1). For these two concentrations, the signal enhancement due to the manganese solution increased with increasing FA, as could be expected from T1-weighting effects, and was maximum for the 1 mM $MnCl_2$ solution. At FA of 60°, the SEs averaged over all slices were equal to 28 % and 22 % for 1 and 10 mM, respectively.

Discussion and conclusions: The objective of this exploratory study was to test the feasibility of using MEMRI for lung imaging. In our conditions, endotracheal administration of manganese resulted in sufficient signal enhancements to visualize the instilled regions. In a previous experiment (4), manganese has proven to be a useful tool to evaluate a pleural tumor when injected intravenously. This study is the first report in which manganese was directly instilled in the lungs to obtain MEMRI images. Our study demonstrated that MEMRI may be used for pulmonary MR imaging. This approach has various advantages: i) it allows for the use of a low concentration of contrast agent (1 mM) compared to a gadolinium-based contrast agent (100 mM), ii) the pharmacokinetics of pulmonary manganese absorption can be evaluated by MEMRI, instead of the use of radioisotopes (5). In addition, the pulmonary route is being investigated for non-parenteral systemic drug delivery. However, a little is known about the fate of inhaled drug delivery systems in the lung (6). Manganese can be incorporated into these carriers and consequently be used to trace drug-loaded particles in the lungs. MEMRI therefore represents an exciting new method for pulmonary imaging in animal models.

References: 1) Beckmann et al. Eur J Radiol. 2007 2) Berthezène et al. Radiology 1992 3) Haage et al. Invest Radiol. 2002 4) Hasegawa et al. Int J Cancer. 2010 5) Heilig et al. Am J Physiol Lung Cell Mol Physiol. 2004. 6) Patton et al. J Aerosol Med Pulm Drug Deliv 2010.