# Lighting-up the lungs: an UTE MRI investigation of the parenchyma signal enhancement due to intra-tracheal administration of an innovative Si-based Gd contrast agent

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**Introduction:**

With the help of Ultra-short Echo Time (UTE) sequences, lung tissue in small animals can be imaged at submillimetric resolution. To further increase the potential of UTE for lung MRI, the intra-tracheal administration (the most direct and effective route for reaching lung tissue [1]) of contrast agent should be envisioned.

In this study we present the MRI investigation of the $T_1$-enhancement of the lung signal due to the *intra-tracheal* administration of different concentrations of an innovative silica-based gadolinium contrast agent, characterized by ultra-small nanoparticles (< 5 nm) and a relaxivity value ($r_1$= 11.4 $mM^{-1}s^{-1}$ at 1.5 T) about three times higher compared to standard DOTA(Gd) and DTPA(Gd) particles. The multimodality imaging characteristics (MRI, CT, SPECT and fluorescence imaging) and the main properties of these nanoparticles are described in details in Ref. [2]. The MRI investigation of the temporal evolution of the signal enhancement is also presented in this study in order to get an estimate of the contrast agent residence time in the lungs.

**Material and methods:**

Protocol: Eight female Balb/c mice (6/8 weeks-old, 20.5 ± 1.5 g), were used for the experimentation. Mice were anesthetized using an intraperitoneal injection of 50 µg/g ketamine and 5 µg/g xylazine. After the acquisition of MR baseline images, an orotracheal intubation was performed on the mice with a 22-Gauge Teflon intravenous catheter. A volume of 50 µl solution of Gd contrast agent was introduced in the lungs through the tracheal catheter. Seven different concentrations were investigated (2, 5, 10, 20, 33, 50 and 100 mM) while saline solution was administrated to a control mouse. After the extubation, MR images of the mice were acquired at different times (from 5 minutes up to several hours after the administration).

MR acquisition: The images were acquired with a 4.7 T Biospec 47/50 spectrometer (Bruker, Ettlingen, Germany), using a transmitter/receiver quadrature coil of 25 mm inner diameter (Rapid Biomedical, Rimpar, Germany). Mice were placed supine in a custom-built plastic holder and kept anesthetized with 2% isoflurane in a mixture of $N_2/O_2$ (80:20) via facial mask. The temperature was kept constant using warm circulating water and the respiratory cycle was monitored constantly. For each animal 6 axial slices of 1 mm thickness were acquired (with an inter-slice distance of 2 mm). The acquisition was performed in *free-breathing* animals, using a 2D UTE sequence (804 directions/128 points, 4 averages) with a TE of 276 µs, FOV of 3 cm. A preliminary study was made in order to optimize the TR and the flip angle (FA). Among the TR explored (14, 50, 84 and 200 ms) a repetition time of 84 ms was chosen as the best compromise between the signal to noise ratio (>35 in the lungs) and the total acquisition time (about 4 minutes); among the FA studied (30, 60 and 80 degrees) a FA of 60° was chosen since it provided good S/N and contrast before the administration of the contrast agent and high signal enhancement after the instillation. These parameters were kept constant during the present investigation.

Image analysis: The images were reconstructed and analyzed with in-house software implemented in IDL (RSI, Boulder, CO). The signal enhancement (SE) was evaluated on three axial slices (top, center and bottom of the lungs) for each mouse. The noise of the image was quantified as the standard deviation of the mean signal of a region of interest selected in the image background. For each image, the lungs were manually segmented to measure the total average pulmonary signal and the signal to noise ratio was computed. The enhancement in each image was computed as the difference between the S/N ratio in the lungs before (baseline images) and after the contrast agent administration, normalized to the S/N of the baseline images [3]. For each mouse the SE was averaged over the three measured slices and the two lungs.

**Results:**

While the SE measured in the control mouse keeps close to zero (-1.6 ± 3.0 %) at different times, few minutes after the contrast agent administration mice presented a significant SE, as shown in Fig. 1 for a 50 mM concentration. The high S/N (>35) achievable in the normal lungs using a very short echo time along with the negligibility of the motion artifacts (typical of the radial acquisition) allowed an accurate quantification of the $T_1$-enhancement effect of the Si-based Gd nanoparticles. The plot of Fig. 2 shows the maximum SE measured for each contrast agent concentration. The SE due to the Gd $T_1$-shortening effect is increasing with the concentration of the contrast agent administrated to the mice up to 50 mM. A maximum SE of 235 ± 15 % was reached with 50 µl of 50 mM solution. For higher values of concentration, the SE is reduced due to the $T_2$* effect, increasing with contrast agent concentrations [3]. In Fig. 3 the temporal evolution of the SEs for the 50 mM solution is shown. The exponential fit provides an estimate of the residence time of the contrast agent administrated intra-tracheal to the mice of about 2 hours and half (τ = 149 ± 51 min). Such a value is related to renal clearance of the contrast agent (data not shown here).

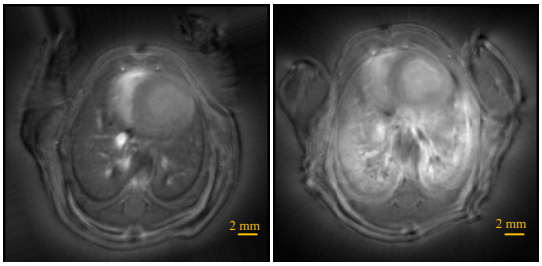
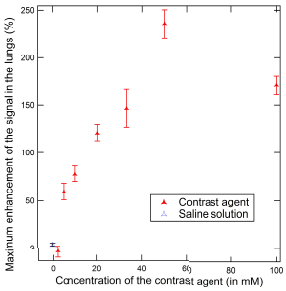



**Fig 1.** One of the 6 axial slices of the mouse lungs before (left) and after (right) the intra-tracheal administration of 50 mM Gd contrast agent.

**Discussion and conclusions:**

This MRI study demonstrates that the innovative contrast agent under study, along with the short echo time typical of the radial acquisition, altogether, allow to obtain notably high signal enhancements (superior to 235% for a 50 mM solution) with relatively small instilled volumes (50 µl). The intra-tracheal administration of the nanoparticles has allowed determining the approximate concentration range for which the signal enhancement is significant and proportional to the concentration (from few mM up to about 50 mM), confirming that the intra-tracheal instillation is a good screening tool for the determination of the dose range that may be appropriate for subsequent studies [1]. The high S/N and the negligibility of motion artifacts, typical of the UTE sequence, permitted the estimation of the residence time of the contrast agent under study. Such a value, of about 2 hours and half, is long enough to allow multiple acquisitions of the animal but short enough to permit the complete elimination from the lungs within half day.



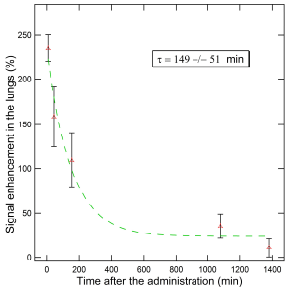




**Fig. 2.** Maximum SE obtained for different concentrations and saline. The values are averaged over the three slices analyzed and the two lungs (mean ± S.E.M). **Fig. 3.** SE temporal evolution obtained with the 50 mM solution (mean ± S.E.M.).

**References:**

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