**Positive contrast ultra-short echo time imaging (UTE) of infiltrating iron-labeled macrophages for early detection of lung inflammation in the mouse**

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**Introduction:** Proton MRI of the lung has often been considered as problematic, because of fast $T_2^*$ tissue relaxation at high magnetic fields. $^1$H-MRI of lung inflammation is limited to stages with beginning edema, while in vivo $^{19}$F-detection of early infiltrating monocytes following application of perfluorocarbons was recently reported (1). In other organs inflammation can be detected by proton MRI after labeling macrophages with superparamagnetic iron oxide nanoparticles (SPIOs). In the lung, however, SPIOs are regarded as useless because of the strong susceptibility effects between lung parenchyma and alveolar spaces. If $T_2^*$ weighting is avoided by the use of ultra-short echo time (UTE) imaging, positive $T_1$ contrast from SPIOs in infiltrating macrophages may be obtained, allowing for early detection of lung inflammation by $^1$H-MRI.

**Materials and Methods:** *Lung phantoms*: Lung phantoms were produced to mimic the alveolar structure. Hot agar gel was mixed with soap and SPIOs to give a foam-like texture containing different concentrations (0.5 to 50 µM) of SPIOs (Resovist and VSOP). *Mouse model*: Bacterial infection was induced in 10 weeks-old C57BL/6 female mice by injecting 100 µl of unlabelled *Staphylococcus aureus* i.v. ($1{,}44 \times 10^8$ CFUs/ml). 2 h and 5 h after infection 5 nm VSOP (Ferropharm) at a concentration of 300 µmol/kg were injected i.v. Mice were imaged 24 h after infection. *MRI*: Measurements were performed with a 9.4 T small animal scanner using an optimized 3D UTE sequence with, TR = 8 ms, TE = 20 µs and a spatial resolution of 0.3 mm$^3$. TR and flip angle (FA) were varied to optimize the positive contrast of the images and also to measure $T_1$. *Histology:* After the MR measurements the animals were sacrificed, lungs were dissected, fixed in a 3.7% formalin solution, and embedded in paraffin. To visualize the iron content, the lung sections were stained with potassium ferrocyanide (Prussian blue).

**Results and discussion:** *Phantoms*: $T_1$ relaxation time decreased from 2084±309 ms for pure foam to 1435±169 ms for a SPIO concentration of 50 µM. UTE signal increased with increasing SPIOs concentration and FA, by up to 49%, indicating that iron can be detected by $T_1$ contrast in lung-like structures. *In vivo*: In vivo, $T_1$w UTE images of the mouse lung (Fig. 1) showed 17% signal increase ($p < 0.001$) for infected mice that had received VSOPs (n = 6), as compared to controls (n = 18), (Fig. 2). No increase was observed for mice that had received bacteria (n = 5) or VSOPs (n = 5) alone. With low-FA UTE and conventional $T_2^*$ and $T_2$ images no significant differences between the groups were observed. Conventional images also did not reveal any signs of inflammation. During section, however, all lungs of infected animals showed clear signs of inflammation (swelling, darker color), while lungs of untreated controls and animals that had received only VSOP appeared normal. Prussian blue staining of the sectioned lungs revealed strong iron accumulations only in animals which had received both, bacteria and VSOP. No such accumulation was observed in controls or animals that had received either VSOP or bacteria alone.

**Conclusion:** Increased signal from SPIO-labeled macrophages in the inflamed mouse lung was observed with $T_1$w-UTE. Lung inflammation could be detected 24 h after systemic application of VSOPs. Positive contrast UTE may open novel applications for SPIO-based molecular MRI.

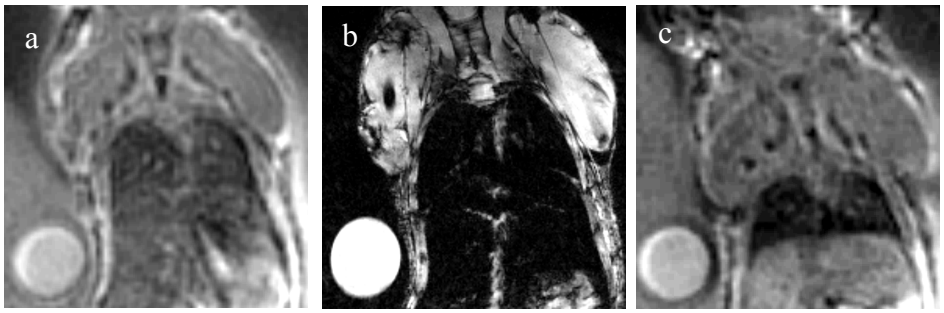


**Figure 1.** Coronal images of the mouse lung of an animal receiving a bacterial infection and VSOPs, a) and b)**: a)** $T_1$w-UTE, **b**) FLASH, and **c)** $T_1$w-UTE of a control animal. Comparison of signal intensities in the lung in a) and c) shows the positive contrast created by SPIOs in the lung.

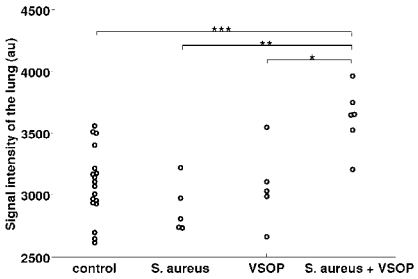


**Figure 2.** Scatter plot shows the signal intensities of the lung of four different groups of mice using $T_1$w-UTE.

**References:** 1.Ebner, B., et al. 2010. Circ Cardiovasc Imaging **3**: 202-210.