P904-USPIO enhanced MR-imaging of ischemic acute renal failure and Cyclosporin A toxicity in a rat model on a clinical 3T scanner

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Introduction:

To assess if the novel ultrasmall particle of iron oxide (P904) can be used to detect and differentiate ischemic acute renal failure (IARF) and chronic Cyclosporin A toxicity (CyAT) in a rat model.

Methods and Materials

In this IRB approved study 32 Lewis-rats were subdivided into three groups. 10 rats in group 1(IARF) underwent transient surgical clipping of the left renal artery for 45 min. 36 h after the surgical procedure the rats were injected 516 µmol/kg P904 (Guerbet) and MR-imaging was performed another 36h after the P904-injection. One rat in group 1 only underwent the clipping procedure but was not given P904. Group 2 consisted of 10 rats which after metabolic priming were fed with high doses of Cyclosporin A (CyA) for 30 days. Group 3 consisted of 10 rats who served as control. In group 2 and 3 516 µmol/kg P904 (Guerbet) was injected and MR-imaging was performed 36h after the P904-injection except for one rat in group 2 which underwent imaging without prior P904 injection. Imaging was performed on a clinical 3T scanner (Siemens TimTrio) with a dedicated 8-element rat coil (RapidBiomedical) with T2w-TSE sequences in coronal (TR/TE 2000/114ms, acquisition time 2:33min) and axial (3090/115ms., 3:47min) orientation with identical acquired spatial resolution of 0.3x0.3x1.0mm³. Signal to noise measurements (SNR) were performed in the cortex, medulla and pyelon of the IARF-kidney, the CyAT-kidneys and the control kidneys. Immediately after the MR-exam the rats were sacrificed for histology with Prussian blue staining to detect iron and immunolabelling for ED1 to detect macrophages.

Results:

There were marked visual differences between the IARF-rats (slightly hyperintense cortex, massive hypointensity of medulla and pyelon), the CyAT-rats (slightly decreased signal intensity throughout cortex, medulla and pyelon) and the control rats (stepwise increasing signal intensity from cortex to pyelon) (Figure 1). The one IARF-rat which was not injected P904 showed a different signal pattern with higher signal intensity in the medulla and pyelon while the rat in the CyAT-group without P904 injection revealed a similar pattern as the P904 positive animals. The mean SNR values of cortex, medulla and pyelon are presented in Table 1. The IARF group showed significantly lower SNRs in the medulla and pyelon ($p<0.000001$), for the CyAT-group only the medulla was significantly different from the control group ($p=0.002$). Abundant iron was histologically found only in the IARF-group predominantly distributed in the medulla. The number of ED1+ macrophages was also highest in the IARF-group (mean 75.1±22.1 per microscopic field of view) compared to the CyAT group (45.6±15.8) and the control group (4.6±2.8).

Conclusion:

P904 seems to be a suitable contrast agent to non-invasively detect ischemic acute renal failure in a rat model with good correlation to histology while P904 – at least at the administered dose – does not seem to be beneficial to detect the lower inflammatory activity of chronic Cyclosporin A toxicity.

	Cortex	Medulla	Pyelon
Control	10.4 ±. 2.3	18.8 ± 3.4	33.7 ± 5.9
IARF	**19.6 ± 5.6**	**4.5 ± 1.0**	**14.5 ± 6.1**
CyAT	11.0 ± 3.5	**15.3 ± 4.9**	24.6 ± 7.1

Table 1: Mean SNR and standard deviations, significant differences marked in bold.

Figure 1:
Display of typical imaging findings in the three different groups. Only in the IARF-group w/ P904 iron positive macrophages were found in the medulla.