In vivo MR imaging of renal ischemia reperfusion injury in mice using microparticles of iron oxide targeting VCAM-1

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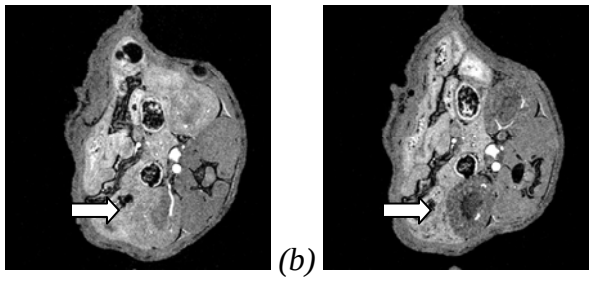
Introduction: Ischemia/reperfusion injury (IRI) is an important cause of tissue damage in vascular syndromes of the heart, brain and kidney. Sensitive tools to image ischemic injury in vivo are lacking. The aim of our study was to investigate whether antibody-conjugated microparticles of iron oxide (MPIO) targeting VCAM-1 would enable molecular magnetic resonance imaging (MRI) of endothelial activation in mouse renal IRI.

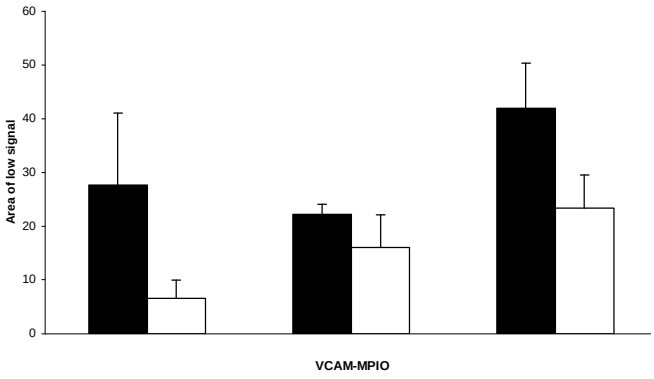
Materials & Methods: In male C57BL/6 mice the left renal pedicle was cross-clamped to induce IRI for 30 minutes. Following a 16-18 hour reperfusion period, the mice were subjected to high-resolution MRI on a 9.4T VNMRS DirectDrive MR system (Varian Inc. USA) using a 33 mm quadrature driven birdcage coil. After scouting, shimming and pulse-calibration, a double-gated, segmented 3D GE-sequence was applied (TE/TR=2.5/4.2ms, 8 k-space lines per cardiac cycle, FOV=25.6x25.6x22mm, 18mm axial slice, flip angle 15°, matrix size 256x256x96, 1 average), followed by tail vein injection of 16µl antibody-conjugated MPIO's in 84 µl PBS, flushed with 100 µl PBS outside of the magnet, but without changing the position of the mouse. The double-gated 3D-GE was repeated 6x, covering a total period of ~90 mins post contrast injection. All 3D data sets were isotropically zerofilled by a factor of 2 and filtered prior to FFT and stored as TIFF images, using purpose written *idl*-software. Areas of left and right kidneys in 5 random slices were subjected to histogram analysis (using ImagePro) as reported previously (1) and the mean pixel density was plotted for both kidneys.

Figure 1:



(a) *(b)*

Figure 2:



Results: Figure 1 shows an axial image through the clamped (arrow) and unclamped kidney (a) pre- and (b) ~60min post contrast injection. The uptake of the contrast agent can clearly be seen in the clamped kidney (Fig. 1b). Although some uptake could also be observed in the normal kidney (clearance by liver or spleen), the initial quantitative analysis demonstrated that the uptake was larger in the clamped kidney (black bars in Fig. 2). No difference in MPIO retention between unclamped and clamped was found when MPIOs were bound to an irrelevant antibody (i.e. IgG, data not shown).

Discussion & Conclusion: This is the first study to report on the non-invasive imaging of IRI in the mouse in vivo using VCAM-MPIO. Importantly, the contrast agent bound specifically and under flow conditions, and the retained MPIO were readily quantifiable from the MR images. Work is in progress to provide a more comprehensive 3D analysis and quantification of the data. In conclusion, our approach provides a platform for non-invasive detection of IRI in the kidney and potentially other organs.

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Reference:

(1) McAteer MA et al, Nat Med 13:1253-1258 (2007).