Timecourse of BOLD response in normal rat kidney following vasomodulator administration using standard 1.5T clinical hardware.

Neil Peter Jerome[1], Jessica K R Boult[1], Matthew Orton[1], James d'Arcy[1], David J Collins[1], Dow-Mu Koh[2], and Simon P Robinson[1]

[1]*CRUK-EPSRC Cancer Imaging Centre, The Institute of Cancer Research, Sutton, Surrey, United Kingdom,* [2]*Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, United Kingdom*

Introduction

Clinical MRI scanners are being increasingly exploited for pre-clinical studies, a reflection of significant hardware advances available on such platforms, and enhanced clinical relevancy. Use of the human-optimised system for small animal work naturally has limitations in resolution, but the use of parallel imaging with existing coils can attempt to bridge the gap from simple volumetric to more functional studies. The use of a small-loop extremity coil, in parallel with a head/neck array allows greater sensitivity to signals arising from small rodents, and allows detection of BOLD changes following administration of vasomodulators such as hydralazine, furosemide and angiotensin II. We demonstrate sensitivity to these challenges in images acquired using standard 1.5T clinical hardware, and the use of this setup to follow the timecourse of the BOLD response.

Experimental

Female Sprague-Dawley rats (n=3) were anaesthetised and a lateral tail vein cannulated with a heparinised 27G butterfly catheter for intravenous administration of agents. MRI was performed on a 1.5T Siemens Avanto scanner, in three sessions at least one week apart. For MR imaging, each animal was secured supine, using an insulating vacuum beanbag to retain body heat and to prevent excessive movement, centered on a small-loop TMJ coil and centered within the multi-element head RX coil. Elements of the head/neck array were used in parallel with the small-loop coil during all acquisitions. BOLD scans were acquired with multiple gradient echo sequence, with echo times 5, 10, 20 30, and 40ms, fat suppression, and parallel imaging factor 2; voxel size was 0.6x0.6 mm in-plane, 5mm slice thickness. A 128x128 matrix was acquired and interpolated to 256x256. Flip angle was 25, with 12 averages, for a scan time of 4 minutes 30 seconds. The BOLD scan was conducted at baseline, and then repeated three times immediately following administration of either hydralazine (5 mg/kg) and furosemide (5 mg/kg), administered as a bolus, or angiotensin II infused at 0.5 µg/min/kg. Images were processed using proprietary software (ADEPT, The Institute of Cancer Research, UK), with ROIs drawn for whole kidney, using anatomic T_2-weighted scans as reference. Scans where significant (through-plane) partial voluming was observed for the kidney were not analysed. Fitting for T_2* used Markov Chain Monte Carlo (MCMC) Bayesian statistical approach [1], with no filtering or smoothing of data.

Results

A typical image, and the corresponding T_2* map, are shown in Figure 1; acceptable resolution was achieved with an appreciable slice thickness, although through-plane voluming precluded segmentation of cortex and medulla; at the longest echo time of 40 ms, the signal approached the noise floor. The median values of T_2* are given in Table 1; baseline values for each challenge were not significantly different ($p > 0.25$, unpaired t-test). Each of the agents caused a measurable and significant change in T_2*, the timecourse of which is shown in Figure 2. Hydralazine caused a decrease in T_2* that became significant after the first post-bolus scan and continued to decrease. Administration of furosemide caused an increase in T_2* that was significant for all time points; at 7 and 11 minutes following the bolus, the T_2* appeared to level off at approximately 48 ms. Angiotensin II caused a decrease in T_2*; the reduction in T_2* was greatest at the first time point, but immediately plateaud, with the T_2* 11 minutes after injection being significantly greater than that at 7 minutes ($p = 0.016$, Wilcoxon signed rank sum test).

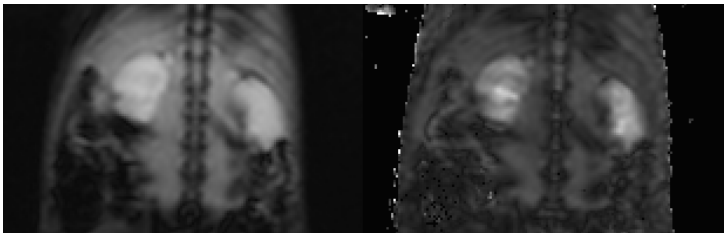

Figure 1: Typical GRE (TE 20 ms) image and T_2* map acquired using parallel combination of TMJ and head coils. In-plane resolution 0.6x0.6 mm, slice thickness 5mm.

Table 1: Average values (ms, mean ± std. error) for median T_2* of whole kidney in successive scans. * indicates $p < 0.05$ against baseline value, and † indicates $p < 0.05$ against previous time point (Wilcoxon).

t (mins)	0	2.25	6.85	11.4
Hyd	37.7 ± 2.0	36.7 ± 2.3*	34.5 ± 1.5*†	30.2 ± 1.4*†
Furo	38.5 ± 2.2	44.7 ± 2.4*†	48.5 ± 2.8*†	47.8 ± 3.0*
Ang	34.5 ± 2.4	29.8 ± 1.9*†	29.4 ± 1.1*	30.7 ± 1.1*†

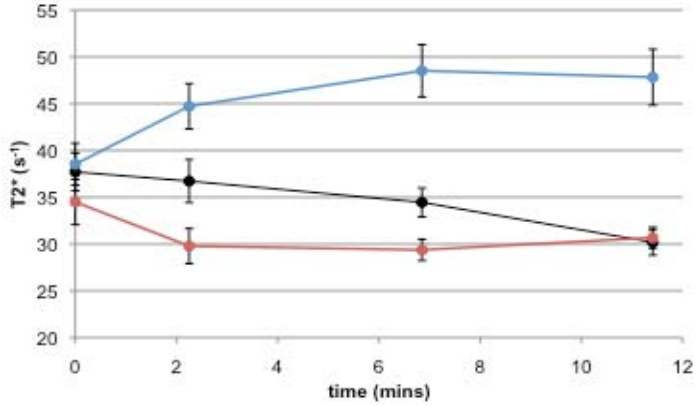

Figure 2: Timecourse of whole kidney median T_2* (n=6) following administration of (black) hydralazine bolus, (blue) furosemide bolus and (red) angiotensin II infusion. Data shown are mean ± s.e.

Discussion

We demonstrate here the ability to successfully image small animals using a parallel arrangement of vendor coils; sufficient signal arises from the combination of extremity and head coils to conduct multiple gradient-echo images within a reasonable timeframe to monitor renal T_2* response to vasomodulation. The effect of hydralazine bolus was a clear decrease in T_2* that continued evenly over the experimental timecourse, consistent with the well-described vasodilatory action of this drug. In contrast, furosemide and angiotensin II challenges appear more difficult to interpret, perhaps due to a more complex mechanism of action. Furosemide is a potent loop diuretic that inhibits reabsorption in the thick ascending loop of Henlé, causing a decrease in renal blood volume which is reflected by this change in T_2* [2]. Angiotensin II is a naturally-occurring hormone and has a complex role within the renal renin-angiotensin system (RAS) [3], and the T_2* decrease observed may be due to a combination of actions including reactive vasoconstriction.

Conclusion

This study clearly demonstrates the use of a conventional clinical imaging platform for pre-clinical BOLD MR imaging of renal physiology, and the longitudinal T_2* response to vasomodulation within the medulla and cortex. Combined with other intrinsic MR imaging biomarkers, this approach will enable a deeper interrogation and understanding of the homeostatic response to vasomodulation, with the potential to be extrapolated to sequential investigations of renal disease and pathophysiology.

References

[1] J. J. Neil *et al*, *MRM* 1993, 29:642-7 [2] S. I. Gomez *et al*, *AJP – Renal Physiol*, 2009 297(4) F981-6 [3] V. Raizada *et al*, *J. Invest. Med.* 2007, 55:341-59

Acknowledgements

We acknowledge the support received for the CRUK and EPSRC Cancer Imaging Centre in association with the MRC and Department of Health (England) (grants C1060/A10334 and C16412/A6269) and NHS funding to the NIHR Biomedical Research Centre.