Drug modulation of ADC and IVIM parameters in the native rat kidney measured using parallel imaging with standard vendor coils on a 1.5T clinical system.

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

[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

Diffusion models of normal kidney are required to account for perfusion components as well as true diffusion; given the highly ordered and heterogeneous nature of the kidney, there is discussion regarding the most appropriate models to use. The Intra-Voxel Incoherent Motion (IVIM) model uses a bi-exponential fitting of the diffusion decay curve to separate true diffusion from 'pseudo-diffusion', representative of perfusion/tubular flow, and has been shown to be suitable for highly vascular organs [1]. In the kidney, it is expected that the pseudo-diffusion term will also contain a tubular flow component. Vasomodulators such as hydralazine (systemic vasodilator), furosemide (diuretic), and angiotensin II (systemic vasoconstrictor) are established as having effects on vascular fraction and flow properties, and so are suitable for testing sensitivity of model parameters to physiological changes. Here we demonstrate response in ADC and IVIM diffusion models to these agents, and show that the sensitivity to these changes is measurable using standard clinical 1.5T scanner hardware.

Experimental

Female Sprague-Dawley rats (n=3) were anaesthetised and a lateral tail vein cannulated with a heparinised 27G butterfly catheter for remote intravenous administration of vasomodulators. Hydralazine (5 mg/kg) and furosemide (5 mg/kg) were administered as a bolus; angiotensin was infused at 0.5 µg/min/kg. MRI was performed on a 1.5T Siemens Avanto. The 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 array were used in parallel with the small-loop coil during all acquisitions. For diffusion studies, coronal images were acquired using 2D EPI sequence, SPAIR fat suppression, TR 2.1 s and TE 71 ms, with 9 b-values (0, 20, 40, 60, 80, 100, 200, 400, 800 s/mm^2), isotropic voxel size 1.5 mm^3, matrix 72 x 72, 18 averages (total time 16 mins) and parallel imaging factor of 2. Images were acquired prior to and ~40 minutes after administration of hydralazine, furosemide, or angiotensin II. DW images were processed using proprietary software (ADEPT, The Institute of Cancer Research, UK), with ROIs drawn for whole kidney, cortex and medulla regions on a per-kidney basis (n=6) using anatomic T_2-weighted scans as reference. Fitting for apparent diffusion coefficient (ADC) used Levenberg-Marquardt algorithm, IVIM curves were fitted using Markov Chain Monte Carlo (MCMC) Bayesian statistical approach [2], with no filtering of data, to derive estimates of vascular fraction f, pseudodiffusion coefficient D* and tissue diffusivity D.

Results

IVIM parameter estimates from fitting diffusion curves are given in Table 1 (mean ± std. error, from median values of ROI); the ADC values correlate with IVIM D in all cases. For baseline parameters, vascular fraction and fD* were significantly higher (unpaired t-test, $p < 0.05$) in the cortex; diffusivity D tended to be higher in the medulla (non-significant). Following hydralazine, all parameters were affected significantly ($p < 0.05$, Wilcoxon signed rank sum test), with the exception of the medulla vascular fraction; increases in f, D*, and fD* were observed, with a larger response in the cortex. The diffusion coefficient D decreased. Following furosemide administration, a decrease in f was not matched in D*, resulting in fD* changing significantly only in the cortex. Diffusion coefficient D increased significantly across the whole kidney. Infusion of angiotensin II resulted in a significant increase in D* in the medulla, with f in the medulla showing a decreasing trend ($p = 0.055$).

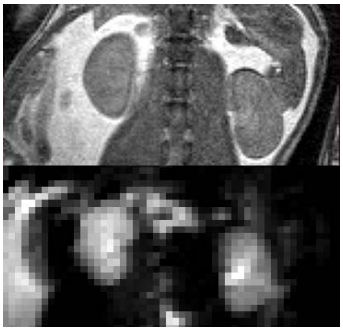

Figure 1: T_2-weighted and DW image (b=100) image obtained using head array and extremity coils in parallel.

Table 1: Parameters from IVIM and ADC model fitting of diffusion curves. Values given are mean (n=6) ± standard error of median ROI values. **bold*** indicates $p < 0.05$, *italic†* indicates $p < 0.1$, from Wilcoxon signed rank sum test. Units: D and ADC (10^{-5} mm^{2}s^{-1}), D* (10^{-2} mm^{2}s^{-1}), f (%), and fD* (10^{-4} mm^{2}s^{-1}).

		Kidney		Cortex		Medulla	
	Challenge	pre	post	pre	post	pre	post
f	Hyd	**10.9 ± 0.7**	**15.1 ± 0.8***	**17.4 ± 2.1**	**24.4 ± 2.6***	7.2 ± 0.8	8.3 ± 1.3
	Furo	*12.0 ± 1.4*	*10.1 ± 1.0†*	**17.1 ± 1.0**	**12.0 ± 1.5***	*9.6 ± 1.7*	*8.2 ± 1.3†*
	Ang	19.1 ± 1.3	18.7 ± 1.3	22.5 ± 2.8	20.9 ± 1.9	*16.3 ± 1.6*	*14.3 ± 1.5†*
D	Hyd	**133.9 ± 5.9**	**100.2 ± 6.6***	**130.3 ± 7.2**	**96.8 ± 8.8***	**139.3 ± 4.0**	**109.6 ± 5.4***
	Furo	**118.8 ± 5.8**	**138.8 ± 5.0***	**117.5 ± 7.7**	**137.4 ± 7.9***	**123.5 ± 5.4**	**141.6 ± 4.3***
	Ang	114.0 ± 7.6	109.8 ± 6.3	113.6 ± 6.8	107.6 ± 5.1	122.8 ± 9.7	116.1 ± 9.0
ADC	Hyd	**130 ± 6.0**	**97.9 ± 7.1***	**126.6 ± 6.5**	**87.9 ± 8.9***	**139.0 ± 4.0**	**111.8 ± 6.2***
	Furo	**117.1 ± 5.8**	**136.2 ± 5.7***	**114.1 ± 9.1***	**134.5 ± 8.6***	**122.7 ± 5.5***	**141.1 ± 5.6***
	Ang	*107.0 ± 7.6*	*105.4 ± 6.4†*	101.9 ± 7.0	100.8 ± 4.2	119.1 ± 10.1	114.1 ± 8.5
D*	Hyd	**4.0 ± 0.2**	**5.0 ± 0.2***	**3.3 ± 0.4**	**5.0 ± 0.2***	**4.3 ± 0.3**	**4.9 ± 0.2***
	Furo	3.6 ± 0.2	3.8 ± 0.1	3.2 ± 0.3	3.7 ± 0.2	3.8 ± 0.2	3.6 ± 0.2
	Ang	4.1 ± 0.5	4.9 ± 0.3	4.0 ± 0.4	4.3 ± 0.3	**4.1 ± 0.6**	**5.0 ± 0.4***
fD*	Hyd	**38.7 ± 1.7**	**65.6 ± 1.9***	**48.1 ± 3.4**	**96.7 ± 9.2***	**25.2 ± 0.9**	**35.6 ± 3.7***
	Furo	38.4 ± 5.0	32.5 ± 3.2	**48.4 ± 5.0**	**37.8 ± 4.3***	29.9 ± 4.7	25.0 ± 2.7
	Ang	66.9 ± 10.6	76.1 ± 10.3	71.4 ± 9.6	77.0 ± 12.4	56.7 ± 10.6	61.6 ± 8.1

Discussion

These results show the sensitivity of the DW imaging method to changes in diffusion and perfusion parameters. Hydralazine effected a clear change in all IVIM parameter estimates for both regions of the kidney; a marked increase in vascular fraction in the cortex is consistent with a vasodilatory action, and an increase in perfusion parameters is consistent with the known effect on renal blood flow [3]. The clarity of these results demonstrates the utility of the parallel imaging arrangement for animal work on clinical scanners using vendor coils. Similarly, sensitivity to furosemide and angiotensin II challenge is evident, although their effects are perhaps more difficult to interpret due to complex mechanisms of action. Following furosemide administration, an apparent decrease in cortical f and fD* was observed, together with a rise in D across the whole kidney. Significant changes (at 10%) following angiotensin II were observed in medulla f and whole kidney ADC; it is possible that homeostatic response to this hormone act to reverse initial response. When considering highly ordered organs such as the kidney, accurate segmentation of regions is critical, and thus a factor in the quality of these observations is the appropriate selection of ROIs. The limited spatial resolution required in order to retain sufficient signal at higher b-values may be expected to lead to partial volume contributions of voxels at 1.5mm^3, and potentially mask differentiation of parameters between regions. Similarly, a greater temporal resolution for acquisition of DW images may reveal more immediate or subtle detail in the response to challenge.

Conclusion

Pre-clinical imaging is viable on a 1.5T clinical system to evaluate the effect of drugs that modulate the IVIM diffusion properties of kidneys; improved understanding of the effects on normal and dysfunctional kidneys could aid drug development in this arena.

References

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