Renal R2 changes and dynamic kidney size variations in response to vasoactive substances in the rat

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Introduction: Relaxation rates, with or without a contrast agent, have been used to obtain a variety of functional information about the kidney, including oxygenation levels, glomerular filtration rate (GFR) and blood volume. Since the kidney is a complex organ, with multiple compartments, relaxation rates may depend on a variety of factors, making interpretation of experimental results complicated. In a previous study [1], we found that, in the absence of a contrast agent, renal R2 values rise slightly in response to adenosine, despite evidence that adenosine increases blood volume. The rise in R2 cannot be explained by the blood volume changes alone, since unenhanced blood has low R2. To probe the additional factors affecting relaxation rate, we further investigated the response to adenosine, and to another vasoactive substance, L-NAME (a nitric oxide synthase inhibitor). In particular we explored the relationship between R2 and kidney size, which appears to vary dynamically.

Methods: Experiments were performed on 15 male Sprague-Dawley rats (262 – 350 g) under an IACUC-approved protocol. In 11 rats the response to adenosine (500µg/kg/min i.v. infusion) was studied, and in 4 rats the response to L-NAME (10mg/kg i.v. bolus) was investigated. Each animal was anesthetized with ketamine (60 – 100mg/kg IP) and Inactin (100mg/kg IP) and imaged on a whole-body 3T Twinspeed system (GE Healthcare, Waukesha, WI) using an extremity coil. A single slice was prescribed through one kidney, and images were acquired using a Carr-Purcell-Meiboom-Gill (CPMG) sequence. In 12 animals (8 from the adenosine group and all in the L-NAME group), imaging was performed in an axial slice with the following parameters: 16 echoes, BW = 62.5kHz, NEX = 4, TR = 1500ms, slice thickness = 3mm, FOV = 8 x 4cm, and nominal matrix size = 256 x 192, giving TE_{min} = 7ms, ΔTE = 7ms, and scan time = 9min 39sec. One rat was imaged as above but in a coronal slice. The remaining 2 rats were imaged in an axial slice but with higher temporal resolution (8 echoes, BW = 15.6kHz, NEX = 1, TR = 1000ms, slice thickness = 4mm, FOV = 6.5 x 3.25cm and nominal matrix size = 192 x 128, giving TE_{min} = 10ms, ΔTE = 10ms and scan time = 1min 6sec). In these two rats, blood pressure was monitored continuously via a cannula in the femoral artery. In the adenosine group, image sets were acquired with adenosine infusion alternately off and on. In the L-NAME group, 3 image sets were acquired at baseline, and 9 image sets following L-NAME administration. The last 6 image sets (30 – 90 min after injection) were used to calculate post-L-NAME values. R2 was obtained by fitting the intensity data as a function of TE to a monoexponential decay using a nonlinear Levenberg-Marquardt algorithm. R2 maps were generated, and R2 estimates obtained for the cortex, outer strip of the outer medulla (OSOM), and inner strip of the outer medulla (ISOM). The cross-sectional area of the kidney was used as an indicator of kidney size and estimated by manually segmenting the kidney from surrounding tissues on the R2 maps.

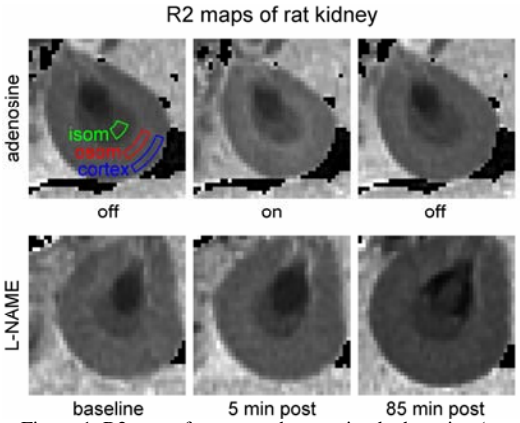

Figure 1. R2 maps from a rat that received adenosine (top row) and from one that received L-NAME (bottom row).

Results: Figure 1 shows R2 maps from two animals, one of which received adenosine, and the other of which received L-NAME. Note that R2 increases in response to adenosine infusion in the renal cortex, OSOM and ISOM (top row), and decreases again when adenosine is switched off. Also, the cross-sectional area of the kidney appears smaller with adenosine on than with it off. The changes in R2 and cross-sectional area were similar for all animals in the adenosine group, including the rat that was imaged in a coronal plane. The coronal images exhibited no significant displacement of the kidney between image sets. In the L-NAME study (bottom row) R2 decreases in all regions over time and the cross-sectional area of the kidney increases. Not all the rats responded equally to L-NAME, but in each case the changes in R2 and kidney size were correlated.

Table 1 summarizes the results for the 12 animals imaged in the axial plane with the 4 NEX (low temporal resolution) sequence. It shows the changes in R2 and kidney size in response to adenosine and L-NAME, and the correlation between the R2 and size changes. Note that the responses to adenosine were all highly significant. The responses to L-NAME were less consistent among the animals, but the correlations between Δarea and ΔR2 in the cortex and OSOM were significant.

Table 1. Group analyses

	ΔR2 in cortex	**ΔR2 in OSOM**	**ΔR2 in ISOM**	**Δarea**
Response to adenosine (mean ± std)	2.8 ± 1.5 s^{-1} **	4.0 ± 1.8 s^{-1} **	2.0 ± 1.3 s^{-1} **	-12.7 ± 2.2 %**
Correlation between ΔR2 and Δarea	r = -0.54	r = -0.76	r = -0.58	
Response to L-NAME (mean ± std)	-2.0 ± 1.8 s^{-1}	-1.7 ± 1.7 s^{-1}	-0.8 ± 2.2 s^{-1}	13.1 ± 8.4 %
Correlation between ΔR2 and Δarea	r = -0.99*	r = -0.99*	r = -0.94	

* significant ($p < 0.05$) ** highly significant ($p < 0.01$)

Figure 2 shows results from one of the rats imaged with high temporal resolution as adenosine infusion is alternately switched on and off. Note that the blood pressure response to adenosine is rapid (<1min). The kidney size changes almost as rapidly (~2min), and R2 varies inversely, but in synchrony, with kidney size. In addition to the adenosine-related changes, there is a gradual drift in both R2 and kidney size over time. The correlations between kidney size and R2 values over time in this rat were very high (r = -0.96 for cortex, r = -0.94 for OSOM and r = -0.80 for ISOM, $p < 0.01$ in all cases).

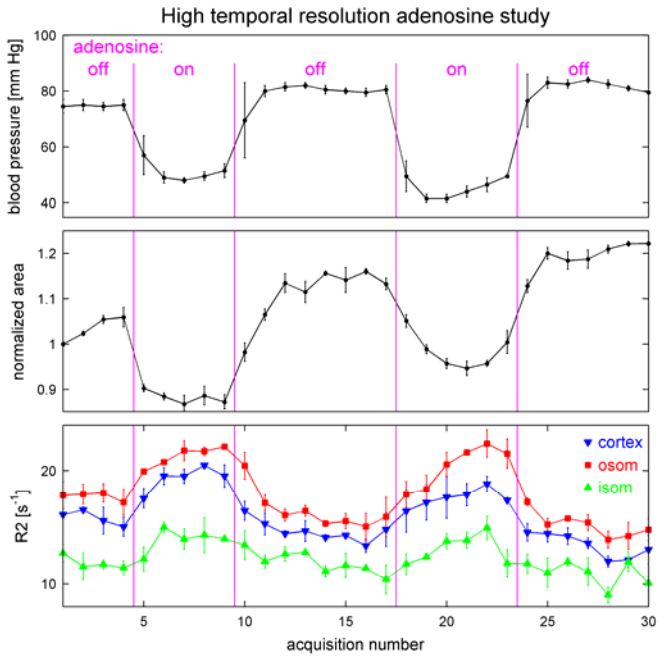

Figure 2. Graphs of blood pressure, kidney area and R2 for one rat as a function of acquisition number. The time for each acquisition is 1 min 6 sec.

Discussion: Although still unclear at this stage, it is possible that the changes in R2 and kidney size may be related to variations in tubular volume. Since filtrate in the tubules has low R2, the effective R2 of the tissue might be expected to vary inversely with filtrate volume. This may explain the inverse relationship we observed between kidney size and R2. Adenosine was found to reduce kidney size and increase R2 values. This may be due to the effect of adenosine on GFR. Adenosine is known to decrease GFR due to preferential constriction of the afferent arteries in the superficial cortex [2]. The volume of the proximal tubules has in turn been reported to be proportional to GFR [3]. The results we observed for L-NAME may be due to its diuretic effect [4]. The higher urine output may increase ureteral pressure, causing dilation of the lumina of the proximal tubules [5]. A gradual increase in ureteral pressure due to bladder filling may also have been responsible for the slow drift in R2 values and kidney size that we observed in the adenosine studies (Figure 2). Other possible contributions to R2 changes may be altered blood flow and oxygenation levels [6]. These findings may have relevance for interpretation of relaxation rates R2 and R2* in other renal studies.

References: [1] ISMRM 2006;1812. [2] Osswald H et al. Circ Res 1978;43:465. [3] Keyes JL et al. Am J Physiol 1971;221:1. [4] Liang M et al. Am J Physiol Renal Physiol. 2001;281:F414. [5] Windhager EE Annu Rev Physiol. 1969;31:117. [6] Dinour D et al. Am J Physiol. 1991;261:F787

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