Dynamic measurement of renal perfusion using CASL: A tool to evaluate the effects of antihypertensive agents in spontaneously hypertensive rats

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Background: Treatment of hypertension via blockade of the Renin Angiotensin System (RAS) is believed to offer superior nephroprotection above other antihypertensive agents (1). In addition to increased renal blood flow (RBF), evidence suggests that improved renal vascular endothelial function, mediated by vasoactive factors such as nitric oxide (NO), may also be an important contributor to the renal protection provided by these agents (2). However, the mechanisms by which various therapeutics and endogenous agents affect renal perfusion are unclear and currently under investigation. Here we describe a non-invasive technique todynamically and quantitatively monitor changes in renal cortical perfusion in rats without the use of exogenous contrast agents. This study uses arterial spin labeling (ASL) to monitor changes in renal perfusion following administration of various pharmacological agents. The objectives were 1) to validate this technique for tracking changes in renal cortical perfusion in response to physiological agents and 2) to investigate the dynamics of renal perfusion in real time following acute administration of an RAS targeting antihypertensive agent. Validation experiments used a known vasodilator Acetylcholine (ACh), and the vasoconstrictor, Angiotensin II (ATII), the main biological product in the RAS pathway. The test compound was the ACE (angiotensin converting enzyme) inhibitor Enalapril.

Methods: All procedures were performed in accordance with IACUC guidelines and approved by the IACUC committee. MR scanning was conducted on a Bruker 4.7T 40cm bore Biospec system. Aged male spontaneously hypertensive rats (SHR), 380-420g, were instrumented with venous catheters for delivery of compounds. Rats were anesthetized with isofluorane and placed supine in the magnet with a 3.5x4cm rectangular transmit/receive surface coil positioned under the kidneys. For validation of this technique, renal perfusion was measured during a pre-infusion baseline, a 20 minute infusion of ACh (4.2ug/min, n=4) or ATII (300pmol/min, n=4), and a post-infusion recovery period. Test groups were dosed with 5.2μM/kg Enalapril (n=6), or saline (n=4). ASL was achieved with continuous labeling in the descending aorta proximal to the renal arteries and 0.8 cm from the detection plane by adiabatic fast passage (3). The pulse sequence consisted of a 5 sec period of labeling followed by a fast 2D gradient echo transaxial image (TR/TE 5.3s/3.1ms, matrix = 128x70, FOV=6 cm, SLTH=4 mm). Interleaved labeled (NA=8) and control (NA=8) images provided dynamic perfusion images at 1.5 minute intervals. Perfusion was calculated from intensities of labeled (M_L) and control (M_C) image pairs for an ROI covering the cortex according to $f=(\lambda/2\alpha T_{1app})(M_C-M_L)/2M_C$, where λ= 0.9ml/g, T_{1obs} = of 1.6s were assumed. Labeling efficiency, α was optimized in a separate group of rats (n=5) using a gradient echo 2D sequence as previously described (4), and an RF power level corresponding to α=0.8 was used for all studies.

Results: Figure 1 demonstrates the robust and reproducible labeling in the aorta in five rats, with an efficiency of α=0.8 achieved routinely. ACh infusion produced a 36 % increase in renal cortical perfusion, while infusion of ATII resulted in a 45 % decrease (figure 2), demonstrating the ability to dynamically track renal perfusion in near real time. Enalapril produced a significant and sustained increase in renal cortical perfusion compared to saline controls (figure 3). A similar increase in RBF has been reported in anesthetized dogs using laser-Doppler flowmetry (5). An advantage with the present technique is its non-invasive nature and the ability to follow the dynamics in near real time. Fitting the response curve for Enalapril challenge to an analytical bi-exponential expression, maximum increase (% from baseline) and time to maximum increase (min) were obtained as 28.09±3.35 % and 49.19±13.0 min respectively, providing a quantitative metric of the dynamics. In a separate study in *conscious* SHRs, the same dose of Enalapril lowered blood pressure significantly compared to controls (data not shown).

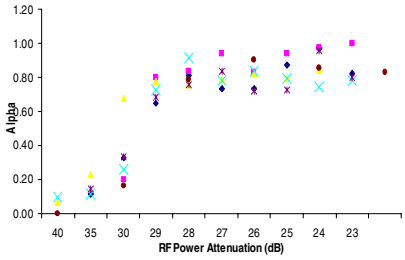

Figure 1. Labeling efficiency for abdominal aorta (n=5).

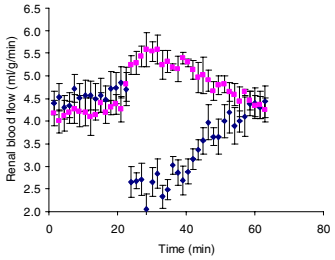

Figure 2. Cortical renal perfusion during 20 minute baseline , 20 minute infusion of AT II (n=4) or ACh (n=4), and 20 minute recovery in rats.

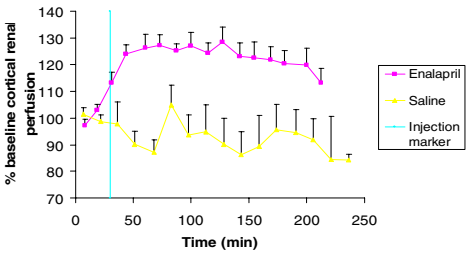

Figure 3. Percent change in renal cortical perfusion in rats following IV administration of 5.2 μM/kg Enalapril (n=6) or saline (n=4)

Conclusion: ASL perfusion MRI provides a non-invasive means of measuring renal perfusion in response to pharmacologic interventions. To our knowledge, this is the first demonstration of quantitative non-invasive measurement of the real time effect of an ACE inhibitor on renal perfusion. This technique offers a tool to evaluate other antihypertensive agents targeting the RAS system and to evaluate the effects of endothelial vasoactive factors, such as NO, on renal perfusion. Since this method provides an absolute measure of RBF, evaluation and comparison of both acute and chronic treatment regimens are possible

References: 1. Delles et al., Kidney International, Vol 61, pp 1462-68, 2002.; 2. Delles and Schmieder, Curr Opin Nephrol Hypertens, 13(5), pp 489-93, 2004.; 3. Williams, et al., Radiology, 190(3), pp 813-18, 1994; 4. Zhang W, et al., Magn Reson Med, 29(3), pp 416-21, 1993; 5. Noguchi et al., Arch Int Pharmacodyn Ther, Nov-Dec: 320, 68-80, 1992.