Arterial Spin Labeled Perfusion MRI in Children with Chronic Kidney Disease

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Introduction: Chronic Kidney Disease (CKD) is associated with numerous systemic changes such as hypertension, atherosclerosis, and anemia that can alter cerebral blood flow and brain function. Patients with CKD are also at increased risk of cerebral ischemia, most notably ischemia affecting subcortical white matter [1]. While many patients develop CKD as a consequence of age-related disorders such as hypertension and diabetes, CKD can also begin in childhood and affect brain development and cognitive function. To further elucidate the pathophysiology and mechanisms of cognitive dysfunction in children with CKD, we are using multimodal MRI to compare brain structure and function in a cohort of children with CKD to controls. Here we report our initial findings using arterial spin labeled (ASL) perfusion MRI to quantify cerebral blood flow (CBF) in this cohort.

Materials and Methods: 29 patients with any stage of CKD I to V (defined as estimated glomerular filtration rate, eGFR <90 ml/min/1.73m2 using modified Schwartz formula, on dialysis, and post-transplant) and 14 age-matched control subjects were included in this analysis. Data acquisition was performed on a Siemens 3T Verio whole body MRI scanner using a 32-channel head coil. A pCASL labeling scheme was implemented with 2D GE EPI sequence. The labeling and control RF duration was 1.5 sec with post-labeling delay of 1.2 sec. Multi-slice perfusion maps were acquired with the following parameters: TR/TE = 4000/17 ms, flip angle=90^0, bandwidth = 1532 Hz/pixel, slice thickness = 4mm with 25% distance factor, matrix size = 64×64, FOV = 240×240 mm^2, slice number = 20, and GRAPPA factor = 2 in Ky. The total ASL MRI acquisition time was approximately 5 minutes for 40 label/control pairs. Absolute CBF maps were calculated using ASLtbx [2]. Gray matter (GM), white matter (WM) and global CBF were extracted using masks created from 3D MPRAGE data. The GM mask was defined by GM probability>0.8 and the WM mask was defined using SM prob>0.8 with erosion. Representative masks are shown in Figure 1. Comparisons between groups (CKD vs. Control subjects) and gender (male vs. female) were applied in measurements of CBF, Hct and age using Wilcoxon rank test. Univariate association between all measurements of CBF, Hct and age were analyzed by using Spearman correlation. Multiple stepwise regression models were used to predict CBF outcomes using group, age and Hct.

Results: Good quality ASL MRI data were obtained from all subjects. An example is shown in Figure 1. Table 1 provides mean ± std values for GM/WM/global CBF along with systemic variables hematocrit, creatinine, eGFR, systolic blood pressure (BP), diastolic BP, age and gender. Patients with CKD showed significantly lower Hct and eGFR as well as higher creatinine as compared with control subjects (P<0.05). We also found a trend of higher GM (P=0.06) and global CBF (P=0.08) in CKD subjects. There was no statistical significant gender difference in CBF. Spearman correlation analyses showed significant univariate associations between five outcomes among the controls (Table 2). CKD showed significant but weaker associations between GM, global CBF, Hct and age but not between WM CBF and age (Table 2). Figure 2 shows a scatter plot of age and WM CBF for CKD and control subjects. For controls there is a significant correlation between age and WM CBF, but in older CKD patients WM CBF appears to be increased. Multiple regression analysis indicated that Hct and age are the dominant predictors of CBF (GM CBF: partial R-square=0.31 and 0.15, P=0.0001 and 0.0021 for Hct and age, respectively; WM CBF: partial R-square=0.28 and 0.12, P=0.0003 and 0.008 for Hct and age, respectively; Global CBF: partial R-square=0.31 and 0.17, P=0.0001 and 0.009 for Hct and age, respectively). There was no significant effect of group status in the multiple regression analysis.

Table 1: Data presented as mean± std

Group	GM CBF (ml/100g/min)	WM CBF (ml/100g/min)	Global CBF (ml/100g/min)	Hematocrit (%)	Creatinine (mg/dl)	eGFR (ml/min/1.73 m^2)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Age	Gender
CKD	81.3±17.6	34.7±6.1	68.1±15.5	36.4±6.7	2.7±2.2	34.0±20.0	117±13.6	69.5±9.2	15.3±3.4	22 M/7 F
Control	70.4±14.9	33.3±7.8	59.9±13.9	40.9±5.8	0.7±0.2	96.7±18.0	110.1±7.8	68.7±8.0	13.4±3.5	5 M/9 F

Discussion: This study demonstrates the feasibility of obtaining quantitative CBF data in pediatric patients with CKD and illustrates the importance of measuring Hct in clinical populations since Hct was the most significant determinant of CBF. In CKD subjects, anemia occurs due to a decrease in the erythropoietin production [3] and anemia reduces blood viscosity, thereby increasing CBF. Severe anemia may also cause in hypoxic complications. This study also confirms significant age effects on CBF in both CKD patients and controls that likely reflect developmental changes in regional brain function. Although Hct and age explained most of the variance in CBF in CKD patients versus controls in the multiple regression analysis, in the univariate analyses CKD patients appeared to deviate from the significant correlation between age and WM CBF observed in controls. While group differences in WM CBF did not reach significance after controlling for Hct and age effects, the finding is of interest because patients with CKD have been reported to have high rates of structural changes in white matter [2], and elevated WM CBF may reflect altered cerebrovascular autoregulation. A larger sample size will be required to validate this preliminary observation and, if it is confirmed, to correlate WM CBF with WM structural lesions
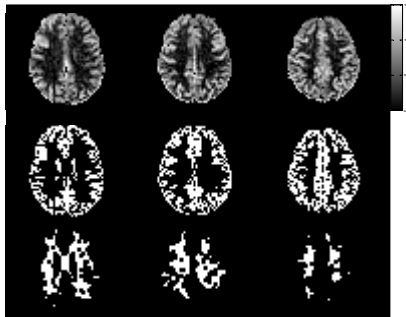
Figure 1. Representative images of CBF maps (upper row), GM (middle row) and WM (bottom row) masks.
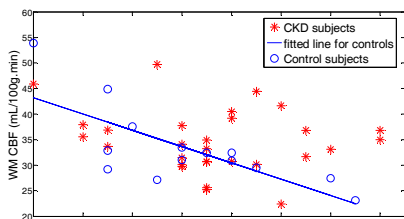
Figure 2. Scatter plots showing correlations between age and white matter CBF in control (blue circle) and CKD (red star) subjects. A significant correlation between age and white matter CBF was found in control (Roh=-0.64, P=0.014) but not in CKD subjects (Roh=-0.13, P=0.494).

	GM CBF	WM CBF	Global CBF	Age	Hct
GM CBF	1.000	0.89 <.001*	0.98 <.001*	-0.85 0.001*	-0.82 0.001*
WM CBF	0.74 <.001*	1.000	0.93 <.001*	-0.64 0.014*	-0.75 0.002*
Global CBF	0.97 <.001*	0.83 <.001*	1.000	-0.83 <0.001*	-0.81 <0.001*
Age	-0.42 0.023*	**-0.13 0.494**	-0.41 0.03*	1.000	0.65 0.012*
Hct	-0.62 <.001*	-0.73 <.001*	-0.68 <.001*	**0.14 0.463**	1.000

Table 2. Spearman correlations for univariate associations between CBF, age and Hct in control (blue font, above the diagonal in the matrix) and CKD subjects (red font, below the diagonal in the matrix). Data are presented as correlation coefficients and P values. *P<0.05. Control subjects show strong correlations for all metrics. No association was found neither between WM CBF and age (Roh=-0.13, P=0.494) nor between Hct and age (Roh=0.14, P=0.463) for CKD subjects.

References: [1] Agildere AM, et al., European Radiology 2001;11(6):1063-9. [2] Wang Z, et al., MRM, 2008, 26:261-9. [3] Kuwabara Y, et al., Kidney International, 2002; 61: 564-9.