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Association of Filtered Sodium Load With Medullary Volumes and Medullary Hypoxia in Hypertensive African Americans as Compared With Whites

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Abstract

Background—African-Americans (AA) develop hypertension earlier with more target manifestations than Whites despite having higher GFR for any level of serum creatinine.

Study Design and Participants—This study tested the hypothesis that increased GFR and sodium reabsorption in AA is associated with increased metabolic work and medullary hypoxia in 49 non-diabetic, essential hypertensive subjects (29 Whites and 20 AAs) taking constant sodium diet (150 mEq/d) and renin-angiotensin system blockade.

Predictors—Ethnicity, age, measured GFR, sodium excretion, and body mass index.

Outcomes—We examined cortical and medullary volumes and blood flows using multi-detector CT and intra-renal deoxyhemoglobin (R2*) using blood oxygen level dependent (BOLD) MR.

Results—Blood pressure and sodium excretion were similar, while AA were more obese and had higher iothalamate GFR. Renal cortical volumes did not differ, but medullary volumes adjusted for body size and age were higher in AA (32.3 ± 11.2 vs 24.9 ± 7.4 cc/m² BSA, $p < .001$). Sodium reabsorption and blood flows were higher in AA. Basal cortical deoxyhemoglobin was similar between ethnic groups, while medullary R2* was higher in AA (39.7 ± 5.1 vs 36.3 ± 6.5 /sec, $p = .02$), but fell to levels similar to Whites after furosemide. The circulating isoprostane prostaglandin F_{2α} was higher in AA and daily urinary prostaglandin F_{2α} excretion in AAs correlated directly with renal blood flow ($R = 0.71$, $p < .01$).

Limitations—Studies were limited to treated, volunteer subjects with normal kidney function without knowledge of prior nutrient intake.

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Conclusions—These data demonstrate for the first time that increased sodium reabsorption in obese, hypertensive AA patients was associated with enlarged medullary volumes, functional hypoxia related to solute reabsorption, and a direct relationship between blood flows and urinary isoprostanes. Our results support a model of increased oxygen consumption and oxidative stress in AA that may accelerate hypertension and target-organ injury compared to white essential hypertensive patients.

Index Keywords

Hypertension; ethnicity; GFR; oxidative stress; BOLD MR; hemodynamics

African-American (AA) patients commonly develop elevated blood pressures at an earlier age than white patients. Target manifestations related to hypertension also appear earlier and can be more severe in African-Americans, including stroke, left-ventricular hypertrophy and congestive cardiac failure ¹. These issues have been amplified by recent trends to increased body weight and obesity particularly prevalent in the Southeastern United States ².

Perhaps unexpectedly, AA patients have higher measured levels of glomerular filtration rate (GFR) using iothalamate as a clearance marker for any level of serum creatinine. This observation led to inclusion of ethnicity as a component of the estimating equations for eGFR based on the Modification of Diet in Renal Disease (MDRD) Study data ³. These equations include a 21% adjustment upward as compared to whites for African-Americans on that basis. Paradoxically, African-Americans have an epidemiologic risk of developing end-stage renal disease (ESRD) at least 3–6 fold higher than whites ⁴. Much of this has been attributed to target injury in the kidney attributable to hypertension (“hypertensive nephrosclerosis”) ⁵, although this mechanism has been questioned ⁶.

Exactly how and whether increased glomerular filtration and high sodium intake are related to increased risk for chronic kidney disease (CKD) is poorly understood ⁷. Some authors suggest that higher filtered loads of sodium in the context of disturbed tubuloglomerular feedback itself can cause a “sodium glomerulopathy” ⁸. We hypothesized that increased glomerular filtration indeed would be associated with increased metabolic work of solute transport, potentially magnifying medullary hypoxia due to oxygen consumption. For these studies, we studied a group of essential hypertensive subjects with normal kidney function identified by ethnicity, i.e. African-American (AA) subjects and white subjects, using a protocol directed at measuring regional kidney volumes, blood flow, tissue oxygenation using blood-oxygen level dependent (BOLD) MR, and urinary markers of generation of reactive oxygen species, such as the isoprostane prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Our results suggest that African-Americans preferentially have expanded renal medullary tissue volumes associated with increased medullary blood flow and oxygen consumption associated with solute transport. Higher oxygen consumption in this group was associated with enhanced medullary hypoxia and urinary excretion of oxidative stress markers.

Methods

Patients

Non-diabetic patients with serum creatinine values less than 1.7 mg/dL with essential hypertension (n=29 white subjects and 20 African-American subjects) were identified from Mayo Clinic (Rochester, MN), the University of Mississippi (Jackson, MS) or the University of Alabama (Birmingham, AL). Informed, written consent was obtained as approved by the Institutional Review Board of the Mayo Clinic. All patients but one were taking either an ACE inhibitor or angiotensin receptor blocker for hypertension throughout the study.

Protocol

A three-day inpatient protocol was performed in the Clinical Research Unit of St. Mary's Hospital, Rochester, MN. Dietary intake was regulated at 150 mEq/day sodium with an isocaloric diet prepared on site. The clinical protocol is depicted in FIGURE 1.

The first study day included measurement of sodium excretion and of determination of measured GFR (mGFR) by iohalamate clearance (iothalamate meglumine, Conray, www.imaging.mallinckrodt.com)⁹¹⁰. Filtered sodium was calculated as the product of serum sodium and mGFR and expressed as mEq/day. Blood pressure (BP) was measured by automated oscillometric recordings including three values taken three times daily.

On the second day, Blood oxygen level dependent (BOLD) MR examinations were performed on a GE Twin Speed Signa EXCITE 3.0T system (GE Medical Systems, www.gehealthcare.com) using an 8 channel torso phased array coil¹¹ as described previously. BOLD-MR imaging consisted of a 2D fast spoiled gradient echo sequence with 8 echo times (TE values) ranging from 2.5 ms to 30 ms. Imaging parameters for the BOLD-MR acquisition included: TR 140 ms, flip angle 45 degrees, slice thickness 5 mm, imaging matrix 224×160–192, field of view (FOV) 32–40 cm, with 0.7–1.0 partial phase FOV. Following the first BOLD-MR acquisition, furosemide (20 mg) was administered intravenously and flushed with 20 ml of saline. BOLD-MR measurements were repeated 15 minutes later at the same locations. A gadolinium-enhanced MR angiogram obtained after BOLD-MR imaging excluded large vessel renal arterial disease.

BOLD-MR images were analyzed on an Advantage Windows workstation version 4.2 using CineTool software (GE Healthcare, www.gehealthcare.com). This program generates a set of parametric images of R2* from the BOLD-MR sequence data by fitting signal intensity data from each echo on a voxel-by-voxel basis to an exponential function describing the expected signal decay as a function of TE and solving for the unknown value of R2*, the magnetic rate of relaxation of the tissue, or the inverse of the T2* relaxation time. R2* reflects the level of deoxyhemoglobin within the regions of interest (ROI) under these conditions¹².

For data analysis, three individual anterior, lateral and posterior ROIs, each approximately 60 mm², were traced in the cortex and medulla manually on the 7-ms TE image or any other image yielding optimal contrast between cortex and medulla, and then propagated to the parametric R2* image to determine average R2* within the ROI. The mean R2* values were calculated for 3 cortical ROIs and 3 medullary ROIs as previously described¹¹.

On the third day of the protocol, the common femoral vein was cannulated with a 6F sheath and blood samples drawn from the right and left renal veins with a 5F pigtail Cobra catheter (Cook, Inc, www.cookgroup.com) for venous levels of plasma renin activity (PRA). The catheter was then advanced into the right atrium for central venous injection of contrast for transit time studies using a multidetector CT, as previously described¹³. A central injection route was chosen to optimize delivery of a contrast bolus for evaluation of transit time and tissue perfusion for both cortex and medulla.

Fifteen minutes after completion of the perfusion study, a kidney volume study (5 mm thick slices) was performed during a contrast injection (0.5 ml/kg up to a maximum of 40 ml, injection rate of 6 cc/s) to determine both cortical and medullary regional volumes as described below.

Image analysis was performed using ANALYZE (Biomedical Imaging Resource Center, Mayo Clinic, www.mayo.edu/bir). Multidetector CT flow studies were analyzed by

selecting ROI in cross-sectional images from the aorta, individual kidney cortex and medulla. The computer then generated curves reflecting the change in tissue density produced by transit of contrast in that region. Regional perfusion, or blood flow normalized per unit tissue (ie, milliliters of blood per minute per cubic centimeter of tissue) was conventionally calculated as: $Perfusion = 60 * \text{Blood volume} / \text{Mean Transit Time} / (1 - \text{blood volume})$, where $(1 - \text{blood volume})$ is a correction for dynamic changes in blood volume that occur *in vivo*¹⁴. Individual kidney mGFR was estimated by assigning the proportion of iothalamate clearance to each kidney according to relative blood flow.

Cortical and medullary volumes were calculated using the stereology module within ANALYZE. ROIs for the cortical and medullary regions were defined on each successive slice (up to 45 slices), and subsequently multiplied by slice width; these were then summed to obtain cortical, medullary, and total renal volume. Cortical and medullary blood flow was calculated as their respective volume $\times$ perfusion, and single-kidney blood flow as their sum.

PGF_{2α} was determined by ELISA (Cayman Chemical, www.caymanchem.com) after extraction on Sep-Pak C-18 columns (Waters Corporation, www.waters.com)¹⁵. Plasma aldosterone and renin activity were measured by radioimmunoassay¹⁵.

Statistical analysis

Results were expressed using mean and standard deviation (SD). Volume measurements were expressed as volume per body surface area in meters squared to adjust for differences in size. Statistical tests were performed using JMP software version 8.1 (1-way ANOVA after confirming normality of sample distributions for kidney volumes, R2* distributions, age and BMI.) Univariate and multivariate models were applied to evaluate mGFR, filtered sodium load, age, BMI, and ethnicity effects on kidney volumes and regional values for R2*. A p-value less than .05 was considered statistically significant.

Results

Demographic characteristics of the two groups submitted to the clinical protocol shown in FIGURE 1 are summarized in TABLE 1. Despite similar duration of hypertension, AA subjects were younger and more obese than whites in this cohort. Treated blood pressures during the protocol did not differ, nor did serum creatinine levels. Numbers and classes of antihypertensive agents did not differ between groups. Measured GFR indexed for body surface area (1.73 m^2 BSA) was higher in AA subjects ($95 \pm 24 \text{ ml/min/1.73m}^2$ vs $78 \pm 19 \text{ ml/min/1.73m}^2$, $p < .001$). Although the filtered load of sodium was higher in AA (FIGURE 2), the 24 hour urinary sodium excretion achieved on Day 1 of the protocol did not differ. Kidney volumes and regional blood flows estimated by multidetector CT were adjusted for BSA and are summarized in TABLE 2. While cortical volumes did not differ (FIGURE 3) medullary volume adjusted for BSA was 30 % larger in AA subjects. Using multivariate models to address differences in mGFR, filtered sodium load, age and body size, medullary volume differed according to ethnicity, whereas cortical volume did not (TABLE 3). Both cortical and medullary blood flows were elevated in AA as compared to Caucasians, as was single-kidney mGFR. Increased blood flow in AA subjects was associated with increased kidney volume and cortical, but not medullary perfusion (TABLE 2).

Intra-renal tissue levels of deoxyhemoglobin measured by BOLD MR, expressed as R2* values, are depicted in Figure 4 (A) and (B). Axial slices that included the renal hilum demonstrated similar levels of cortical R2* values for both AA and Caucasians. As expected, medullary R2* was higher than cortex for both groups. Medullary R2* values were higher in AA subjects than Caucasians (39.7 ± 5.1 vs 36.3 ± 6.5 /sec, $p = .02$). Using multiple regression analysis, medullary R2* levels were predicted by ethnicity, but not age,

medullary volume (after allowing for ethnicity) or body mass index (BMI). mGFR or filtered sodium did not relate to R2* within medulla in either univariate or multivariate models, although it was a prominent predictor for cortical R2* values. (TABLE 3) When repeated after furosemide, cortical levels did not change, but medullary R2* levels fell to the same level in both groups. Post-furosemide values were not correlated to age, body size, regional volumes or blood flow.

Levels of PRA, aldosterone, and urinary isoprostanes measured on Day 1 of the study protocol are summarized in TABLE 1 and FIGURE 5. Renal vein renin measurements on day 3 confirmed that no lateralization (side-to-side ratio ≥ 1.5) was present in any subject. Blood glucose and lipid levels did not differ overall. PRA tended to be lower in AA subjects ($p=.08$) despite administration of ACE inhibitors and diuretics to both groups. Circulating isoprostanes (inferior vena cava) were higher in AA subjects (TABLE 1). Urinary isoprostane excretion demonstrated a positive correlation with blood flows (total renal blood flow, cortical and medullary blood flow) in African-American subjects ($R=0.71$, $p<.001$) whereas no such relationships were evident in Caucasian subjects (FIGURE 5) The differences between ethnic groups persisted after adjustment for BMI and filtered sodium load.

Discussion

These data demonstrate that hypertensive African-American subjects had disproportionate elevation in renal medullary volume and blood flows as compared to Caucasians, even after allowing for differences in age and body size. Elevated medullary volume was characterized by higher levels of deoxyhemoglobin (as reflected by R2*) under basal conditions, consistent with more extensive oxygen consumption in deep medullary segments that reversed after administration of furosemide. We interpret this response to furosemide primarily to reflect oxygen consumption related to tubular solute transport under these conditions, consistent with reabsorption of a high filtered sodium load¹⁶. Unlike Caucasians, higher blood flows to the kidney in African-Americans were related to urinary excretion of PGF_{2 α} , suggesting that high oxygen consumption in turn increased generation of stable products of oxidative stress.

Previous studies suggest that hypertension in African-Americans is associated with earlier onset and more severe target manifestations¹¹⁷. Measurements of renal hemodynamics and function have produced widely varied results, often depending upon conditions of sodium intake and/or medications. Our results extend those of Parmer and colleagues, who identified no differences in untreated subjects during low sodium intake, but identified increased GFR during “high” (ad libitum, measured output 155 mmol/d) sodium intake similar to the levels in our protocol¹⁸. Our studies were performed during continued antihypertensive therapy with agents that block the renin-angiotensin system. We employed this strategy because angiotensin II is known to modulate renal hemodynamics and may affect efficiency of sodium transport and associated oxygen consumption^{19;20} and BOLD MR signaling²¹. To minimize this variable for these studies, we elected to continue treatment in all subjects. Because experimental diabetes also is known to affect tissue oxygenation in the kidney, our studies excluded individuals with identified diabetes mellitus. As expected, the African-American subjects were younger than Caucasians although reported duration of hypertension (not shown) was similar. As a group, the AA subjects were more obese than the Caucasians studied. We cannot exclude an additional confounding role for obesity in AA that may increase both blood flows and GFR^{22;23}. However, no independent effect of body mass index (BMI) was apparent in multivariate analysis, and treated blood pressure levels, sodium intake and output, and metabolic parameters were otherwise similar between the two groups.

Our data using BOLD MR confirm and extend observations that a sizable gradient develops between cortical levels of deoxyhemoglobin (with low $R2^*$ levels) and deep medullary segments (higher $R2^*$ levels). These levels are consistent with measurements in normal subjects and essential hypertensive subjects as previously reported from our center and others using 3-Tesla magnetic fields^{11;24;25}. Pruijm and colleagues demonstrated a rise in medullary $R2^*$ values in normal subjects undergoing an increase from low to high sodium intake²⁵. Experimental studies using oxygen-sensitive probes confirm substantial and progressive decrements in tissue oxygenation and rise in deoxyhemoglobin within the ranges observed here as a result of changes in blood flow and solute transport^{12;20;26}.

A major new observation in this study is that while cortical oxygenation did not differ between Caucasian and African American hypertensive subjects, $R2^*$ levels in medullary segments were higher in AAs, suggesting that these kidneys were functioning at more extreme levels of deoxygenation, despite high levels of blood flow. These data are consistent with higher filtered sodium loads in AAs with higher solute reabsorption required to maintain sodium balance. Our results indicating that $R2^*$ levels fell to similar levels with Caucasians after furosemide indicate that these changes represent a functional level of oxygen consumption primarily related to solute transport^{27;28}.

We interpret these results to suggest that medullary segments in AA subjects were in fact consuming more oxygen, thereby leaving medullary segments relatively more “hypoxic” as compared to Caucasian subjects. These results provide an additional physiologic mechanism generally consistent with the theoretical model proposed by Aviv and colleagues related to a proposed “sodium glomerulopathy”⁸ in African Americans. Our results provide an additional metabolic framework for considering the hazards of “hyperfiltration” beyond those associated with alterations in glomerular filtration pressures. It is known that the normal kidney generates regional oxygen gradients based on solute reabsorption that are closely regulated²⁹. Even sustained reductions in main renal artery blood flow sufficient to reduce glomerular filtration, lead to functional adaptation for metabolic work capable of preserving regional tissue oxygenation¹³. Our results indicate that one consequence of glomerular “hyperfiltration” is delivery of high filtered loads of sodium to energy-requiring tubular reabsorptive sites. The energy requirements to reabsorb these high solute loads were associated with more severe tissue deoxygenation, measured here as high medullary $R2^*$ values (FIGURE 4).

The implications of large medullary volumes and extreme tissue deoxygenation in stable human subjects are not known. Our results suggest that the level of blood flows to the kidney in AA—both in cortex and medulla—were correlated with urinary $\text{PGF}_{2\alpha}$ level. This marker of oxidative stress reflects excessive generation of reactive oxygen species capable of accelerating tissue injury in many experimental models^{30;31;32}. No such relationship was evident in Caucasian subjects under the same protocol conditions. Previous studies indicate that hypertensive African-Americans with varied kidney disorders are demonstrably more “salt-sensitive”⁷ and have higher circulating markers of tissue injury and repair, such as $\text{TGF}\beta$ ³³. We consider it plausible that increased oxidative stress in deep medullary segments eventually may contribute to small vessel injury and tissue fibrosis, as observed elsewhere^{15;30;34;35}. Kidney function was preserved in our patients and urinary total protein levels were normal, although many of these subjects were obese and had modestly elevated microalbumin excretion. Whether obesity, ethnicity or other factors were paramount in defining the relationship between oxidative markers and blood flow cannot be resolved with the present data.

Previous studies suggest that a predilection to renal injury is present in AA subjects as a consequence of low birth weight and reduced nephron number^{17;36}. We have no direct

measure of nephron number or accurate birth weight in our subjects and cannot exclude this possibility. Inasmuch as renal cortical volume may be an index of nephron number³⁷, it was not decreased in our patients.

Is it possible that these data reflect a “phenotype” of pre-existing renal structural abnormalities related to a genetic abnormality highly prevalent in the African-American population, as recently proposed^{38;39}? Subtle renal abnormalities also have been postulated to account for “salt-sensitive” hypertension⁴⁰. Our subjects were hypertensive at a young age, but had no other overt stigmata of kidney disease. Although total urinary protein excretion was within normal limits, urinary microalbumin levels were above normal in both white and AA cohorts. These levels suggest early renal abnormalities and elevated cardiovascular risk for some of these participants.. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that differences in health behaviors alone between whites and AA’s do not explain the disparities in hypertension prevalence and control⁴¹. We believe it possible that genetic segregation of renal traits may include structural differences in medullary size and hemodynamics that predispose to glomerular injury and focal glomerular sclerosis^{38;39}. Whether medullary volumes and sodium reabsorption might have been “pre-conditioned” by higher dietary sodium or other solutes constituents cannot be established by the present data. We believe it to be possible that previous exposures to sustained high sodium intakes may favor medullary expansion. The potential for sodium restriction to reduce medullary deoxygenation in this cohort merits further study.

These studies were necessarily limited to individuals without evident kidney injury who agreed to participate. AA subjects were not specifically matched by age or body weight although precautions were taken to exclude diabetes. No verifiable information regarding prior nutrient intake was available, although dietary intake during protocol evaluation was carefully monitored. Care was taken to adjust for differences in mean age and body size in data analysis and presentation.

Taken together, our studies extend observations regarding tissue oxygenation using BOLD MR to examine within the gradients developed in kidney tissue. They argue that the robust ability to recover and transport sodium and chloride is associated with enhanced energy consumption that ultimately may be associated with generation of reactive oxygen species in African American subjects. Whether this provides an avenue to identify patients at risk for progressive kidney injury and a potential site for intervention warrants further study.

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Regulated diet of 150 mEq/d sodium; patients continue with any prescribed ACEi/ARB/diuretics

Figure 1.

The 3-day clinical protocol utilized to characterize mGFR, isoprostane excretion, medullary and cortical oxygenation (by BOLD-MR) and blood flow (by multi-detector CT) in white and African-American hypertensive subjects. Patients were treated with agents to block the renin-angiotensin system and dietary sodium intake was maintained at a constant level (150 mEq/day).

Figure 2.

Daily filtered load of sodium (serum sodium concentration × glomerular filtration rate) expressed in mEq/day. Despite identical dietary intake and excretion of sodium in the Clinical Research Unit, daily filtered sodium was higher in AA subjects due to increased GFR, indicating higher net tubular sodium reabsorption in AA patients.

Figure 3. Cortical and medullary tissue volumes (expressed as cubic centimeter (cc) / m² (BSA) in essential hypertensive patients. Although overall kidney sizes were only slightly larger in AA subjects and cortical volumes did not differ, medullary kidney volume was substantially larger than in whites.

Figure 4.

(A) Examples of axial slices at the renal hilum with BOLD-MR parametric maps depicting cortical and medullary regions in a white subject (upper panel) and African-American (lower panel). Medullary volumes and $R2^*$ levels (reflective of deoxyhemoglobin level) were higher in AA subjects. (B) BOLD-MR measurements in kidney cortex and medulla in Caucasian and African American subjects during constant sodium (150 mEq/d) intake. Cortical $R2^*$ levels were lower than medullary levels in all subjects, but did not differ between ethnic groups. By contrast, medullary $R2^*$ was higher in AA subjects under initial conditions (pre), but fell to the same level after inhibition of solute transport with furosemide (post). No change in cortical $R2^*$ was evident after furosemide in either group.

Figure 5.

Even after adjustment for filtered sodium load, daily excretion of urinary isoprostanes was correlated directly to measured renal blood flow in African-American subjects, but not in whites.

Table 1

Clinical and demographic characteristics

	Caucasian (n=29)	African-American (n=20)	ANOVA P
Age (years)	64 (20–85)	52 (28–75)	p<.001
Systolic BP (mm Hg)	136±19	135±16	p=.8
Diastolic BP (mm Hg)	71±13	78±10	p=.05
Weight (kg)	78±14	87±22	p=.02
BMI (kg/m ²)	27.3±4.3	32.0±7.0	p=.005
Sex (male:female)	18:11	5:15	
Creatinine (mg/dL)	0.98±.26	0.86±.31	p=.2
mGFR (ml/min/1.73m ²)	78±19	95±24	p<.001
Urine sodium (mmol/24h)	169±45	176±60	p=.7
PRA on day 1 (ng/ml/h)	6.1±7.7	3.1±4.5	p=.2
Glucose (mg/dL)	101±16	95±12	p=.3
Total cholesterol (mg/dL)	183±30	206±37	p=.05
Aldosterone (ng/dL)	3.9±1.5	3.5±1.6	p=.3
Urine protein (mg/d)	90±78	120±293	p=.6
Urine microalbumin (mcg/d)	31±40	73±251	p=.4
Plasma isoprostane PGF _{2α} (pg/ml)	101±67	153±150	p=.006
No. of BP medications per patient	2.9±1.2 *	2.4±.8 **	P=.09
Taking ACEi or ARB	29/29	19/20	
Taking thiazide-class diuretic	23/29	18/20	

Continuous variables are given as mean (range) or Mean±Standard Deviation.

Conversion factors for units: creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; glucose in mg/dL to mmol/L, $\times 0.05551$; cholesterol in mg/dL to mmol/L, $\times 0.02586$; PRA in ng/ml/h to ng/L/s, $\times 0.2778$; aldosterone in ng/dL to nmol/L, $\times 0.0277$.

ANOVA, analysis of variance; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; PRA, plasma renin activity; BMI: body mass index, mGFR, measured glomerular filtration rate; PGF_{2α}, prostaglandin F_{2α}

* range, 1–5

** range, 1–4

Table 2

Single Kidney Volume, Perfusion and Blood Flow

	Caucasians (n=29; 58 kidneys)	African-Americans (n=20; 40 kidneys)	ANOVA P
Kidney volume			
Total volume (cc/m ²)	75±15	83±18	P=.02
Cortex (cc/m ²)	49.8±11.9	50.6±10.0	p=.7
Medulla (cc/m ²)	25.1±7.4	32.3±11.2	p<.001
Tissue Perfusion			
Cortex (mL/min/cc tissue)	3.48±1.04	3.97±0.83	p=.02
Medulla (mL/min/cc tissue)	1.33±0.49	1.41±0.28	p=.4
Blood Flow ^a			
Total renal (ml/min/m ²)	207±78	248±73	p=.02
Cortex (ml/min/m ²)	174±72	204±66	p=.05
Medulla (ml/min/m ²)	32±23	45±17	p<.001
Venous PO ₂ (mmHg)	60±9	64±11	p=.08

Values shown are Mean ± Standard Deviation, and are normalized by body surface area in m²
 ANOVA: Analysis of variance; PO₂, partial pressure of oxygen

^a_{(volume × perfusion)/m²}

Table 3

Univariate and Multivariate analysis of kidney volumes and Tissue oxygenation

		Univariate		Multivariate	
		Parameter estimate	p-value	Parameter estimate	p-value
Kidney Volume/m ²					
Medulla/m ²	Ethnicity	7.35	.0003	6.39	.006
	Age	-0.17	.008	-.0059	.9
	BMI	.06	.7	-.38	.05
	mGFR	.21	.001	.20	.01
	Sodium	-.029	.7		
Cortex /m ²	Ethnicity	.81	.7	-4.53	.05
	Age	-.198	.01	-.031	.7
	BMI	.07	.7	0.46	.02
	mGFR	.41	.0001	.55	.0001
	Sodium	-.13	.2		
Tissue R2* levels at baseline ^a					
Medullary R2* (/s)	Ethnicity	2.89	0.04	3.87	.03
	Age	-.02	0.5	.047	.3
	BMI	-.10	.4	-.23	.1
	Medullary volume/m ²	.159	0.03	.097	.2
	mGFR	.011	.8	.0023	.9
	Sodium	.056	.3		
Cortical R2* (/s)	Ethnicity	.29	.6	1.01	.2
	Age	.0043	.8	-.022	.3
	BMI	-.026	.6	.050	.4
	Cortical volume/m ²	-.072	.006	-.01	.8
	mGFR	-.068	.001	-.0969	.003
	Sodium	.024	.4		

After adjustment for body surface area, body mass index (BMI), age, measured glomerular filtration rate (mGFR) and sodium, medullary volumes differed by ethnicity, whereas such a difference was not significant for cortical volume. Medullary R^2 * levels differed by ethnicity and medullary volume in univariate comparison, although only ethnicity remained after adjustment for age, BMI, medullary volume and mGFR. Cortical volume varied inversely with age, although showed no overall dependence on ethnicity, age or BMI in multivariate models. Cortical R^2 * levels varied inversely as a function of mGFR, with no evident role for ethnicity, age or BMI.

^a R^2 * is a measure of tissue oxygenation, and is determined by BOLD MR.