Long-Term Effects of Kidney Donation on Renal Function and Blood Pressure in African Americans

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Summary

Background and objectives African Americans (AAs) have four times higher prevalence of ESRD than Caucasians. Therefore, long-term effects of kidney donation are of considerable importance in this patient population.

Design, setting, participants, & measurements GFR was measured by $^{125}$I-iothalamate clearance, 24-hour urine albumin excretion, and 24-hour BP monitoring in 33 AAs and 11 CAs who donated kidneys for transplantation 5 to 23 years previously.

Results Mean GFRs were 76 ± 11 and 78 ± 11 ml/min per 1.73 m² for AA and CA donors, respectively. Nine percent of the AA donors and none of the CA donors had GFRs below 60 ml/min per 1.73 m². AA donors had a tendency for lower prevalence of microalbuminuria compared with CA donors (18.1% versus 36.3%) and a tendency for higher prevalence of macroalbuminuria compared with CAs (12.1% versus 0.0%). Twenty-four percent of the AAs, and 45% of the CAs were hypertensive with mean daytime BP ≥135/85 mmHg. Only 6% of AAs had a decrease in mean nocturnal systolic BP of 10% or more as compared with daytime readings. Older age at time of donation was associated ($P = 0.046$) with lower GFR values compared with younger ages.

Conclusion Carefully selected AA kidney donors have well preserved renal function and a low prevalence of hypertension many years after kidney donation. Abnormal albumin excretion and loss of physiologic decrease in nocturnal BP is more prevalent in AA donors than the general AA population. Older age at donation may predict lower GFR after donation.

Introduction

Kidney transplantation from living donors is the best therapeutic option for most patients with ESRD (1). The realization that kidneys from unrelated living donors have superior survival to kidneys from deceased persons expanded the donor pool significantly (2) and has resulted in the largest increase among living donors as reported by the Scientific Registry of Transplant Recipients. The donor exchange program is likely to increase the number of living donors even further (3). However, the increased number of living donors has raised concerns about the long-term safety of kidney donation (4). Although extensive renal ablation in certain animal models leads to glomerulosclerosis, proteinuria, and progressive azotemia, it has been demonstrated in the Caucasian population that uninephrectomy for kidney donation does not increase the risk of ESRD or mortality (5). Furthermore, the data also indicate that the incidence rates of albuminuria and hypertension do not differ between these donors and matched controls with two kidneys. It appears that the loss of substantially more than 50% of nephron mass is required in Caucasians before adverse consequences develop. Some data even indicate that kidney donors live longer than the general population, although this is probably attributable to predonation selection of healthy persons (6).

In contrast, there is very limited information on the effect of 50% decrease in kidney mass on kidney function and BP in African Americans (AAs). One small study from the University of Alabama found that, after a mean follow-up of 6 years, AA kidney donors had higher mean arterial pressure compared with Caucasian donors, with no difference in proteinuria and kidney function (7). Recently Nogueira et al. (8) reported a 41% prevalence of hypertension in AAs 7 years after kidney donation.

AAs have four times higher prevalence of ESRD than Caucasians, and most renal diseases have a more aggressive course and faster loss of kidney function in AAs (9). The effects of decrease in renal mass by kidney donation are thus of considerable importance in this patient population. The primary goal of this study was to evaluate the long-term safety of kidney donation in AAs. We also compared the AA safety profile to that observed in a Caucasian population, by
comparing GFR, creatinine clearance (CrCl), serum creatinine concentration, urine albumin excretion (micro/macro albuminuria), and BP in these AA and Caucasian donors 5 to 23 years after kidney donation.

Materials and Methods
A cross-sectional cohort of study subjects was selected by identifying the pool of kidney-transplant recipients who received their kidney from a living related donor at the Medical University of South Carolina (MUSC). At the time of initiation of the study, a total of 133 AAs had donated a kidney 5 or more years earlier. In compliance with our institutional review board, we used AA kidney transplant recipients to provide contact information for their respective donors. Many recipients were unable to be contacted by study personnel (n = 52), provided incorrect donor contact information (n = 25), or did not respond to phone calls or letters (n = 14). Some donors who were contacted refused to participate (n = 8), and one donor had died of non-kidney-related causes. Ultimately, we were able to enroll 33 (11 men and 22 women) AA donors (Table 1). In all of the subjects, donor nephrectomy had been performed using an open surgical approach. In a similar manner, we also recruited 11 Caucasian donors (five men and six women) for comparison with the AA group. We attempted to match the Caucasian donors to the AA donors as closely as possible with regard to length of interval since donation and age of the donor at the time of donation. We also attempted to ensure that the gender distribution in the Caucasian group was similar to that of the AA group, but given the constraints of the first two criteria, the Caucasian group was slightly skewed from the 2:1 woman-to-man ratio present in the AA sample.

The study was performed in the inpatient General Clinical Research Center of MUSC, where a clinical evaluation was conducted on each consenting participant. The evaluation included medical history and physical exam, basic blood chemistries, GFR measurement, 24-hour urine collection for creatinine clearance, microalbuminuria and proteinuria, and 24-hour BP monitoring. The study was approved by the institutional review board at MUSC.

GFR was measured by 125I-iothalamate (Questcor Pharmaceuticals Inc., Union City, CA) clearance. In brief, before the test the study subject was asked to empty his/her bladder completely, and the collected urine served as background urine. The 125I-iothalamate was injected subcutaneously in the amount of 35 μCi. Thirty minutes before iothalamate injection, participants received an oral dose of saturated solution of potassium iodide and 10 ml/kg water load. Hydration with water was continued at the rate of 200 to 400 ml/h for the duration of the GFR determination. Starting at least 60 minutes after 125I-iothalamate injection, urine and blood samples were collected for four or five 30-minute periods. Urine flow was determined for each 30-minute period, and serum and urine samples were counted in a 1261 Multigamma gamma counter (LKB Wallace, Gaithersburg, MD). GFR was calculated using a standard formula, and the mean from four or five determinations was interpreted as a subject’s GFR. Microalbuminuria was defined as urine albumin excretion between 30 and 300 mg/24 hours. Macroalbuminuria was defined as urine albumin excretion over 300 mg/24 hours.

Twenty-four-hour BP data were obtained with a Spacelab model 90207 ambulatory oscillometric monitor (Spacelab Healthcare Inc.) with 30 minutes of daytime and 60 minutes of nocturnal interval recording. Hypertension was defined as daytime mean ambulatory BP greater than 135/85 mmHg. A subject was classified as nondipping if the difference between the mean nighttime and mean daytime BP (systolic [SBP] or diastolic [DBP]) was less than 10%.

Statistical Analyses
Donor characteristics (demographic and clinical) were summarized for AAs and Caucasians using means and 95% confidence intervals, along with medians and interquartile ranges. Although the study was only powered to detect large differences between the two race groups, we did compare the groups using nonparametric Wilcoxon rank sum tests and χ² tests, as appropriate. Because the comparisons between AAs and Caucasians were largely investigatory in nature, we did not adjust any of the P values for multiple comparisons. All of the analyses were run in SAS v9.2 (Cary, NC) or R, and P values < 0.05 were considered statistically significant.

To determine whether the association between subjects’ time interval since donation and their renal function (i.e. GFR, micro/macro albuminuria, SBP, DBP, and dipping status) differed significantly between AAs and Caucasians, we constructed a series of linear and logistic regression models, with the renal function and BP parameters serving as the dependent variables of interest. In these models, we included the subject’s race, the time since donation, and the interaction between race and time since donation, with the interaction term serving as the primary independent variable of interest. Because of multicollinearity between the subject’s time interval since donation and the age at donation and age at time of study, we repeated these analyses using these age variables in lieu of time since donation. We then constructed a series of additional regression models for the AA study population alone to examine the effect of donor characteristics (including gender, age at donation, age at time of study, and time interval since donation) on renal function and BP parameters. Again, separate models were examined for the age/time variables because of their multicollinearity.

Results
Demographic data on AA and Caucasian donors are presented in Table 1. There were no significant differences in the age at donation, age at study, interval time from donation to study, or body mass index between AA and Caucasian donors. The subjects were predominantly female, with the median ages at donation being 31.0 and 34.0 years and ages at the time of the study being 42.0 and 45.0 years for AAs and Caucasians, respectively. The subjects in general were overweight or obese, because the median body mass indices were 30.9 and 27.9 for AAs and Caucasians, respectively.

Renal function characteristics, including GFR, CrCl, serum creatinine concentration, and urine albumin excretion status as measured at the time of the research study, are
summarized in Table 2. No statistically significant differences were noted between AAs and Caucasians in any of these measurements. The mean (± SD) GFRs at the time of study were 76 ± 13 and 78 ± 11 ml/min per 1.73 m² for AA and Caucasian donors, respectively. Three (9%) of the AA donors and none of the Caucasian donors had GFR below 60 ml/min per 1.73 m². The mean CrCl values at the time of the study were 96 ± 20 ml/min and 108 ± 42 ml/min for AA and Caucasian donors, respectively, and the mean serum creatinine concentrations were 1.1 ± 0.2 and 1.0 ± 0.2 for AA and Caucasian donors, respectively.

The prevalence of microalbuminuria and macroalbuminuria in AA and control Caucasian donors is also presented in Table 2. Although no statistically significant differences were noted, AA donors had a tendency for lower prevalence of microalbuminuria compared with Caucasian donors (18.1% versus 36.3%) and a tendency for higher prevalence of macroalbuminuria compared with Caucasians (12.1% versus 0.0%). Spearman correlations indicated a strong and significant association between GFR and CrCl (rho = 0.50, P < 0.001), but not between any other pair of renal function measures.

Twenty-four-hour ambulatory BP data are summarized in Table 3. AAs had significantly (P < 0.05) lower daytime DBP and mean arterial pressure (MAP) measurements when compared with Caucasians. No other BP measurements were significantly different between race groups. Eight (24%) of the 33 AAs and five (45%) of the 11 Caucasian donors had daytime SBP > 135/85 mmHg. Only one (3%) AA donor reported taking BP medicines compared with 36% Caucasians (P < 0.01). Only 6% of AAs and 0% of CAs had a decrease in mean nocturnal SBP of 10% or more as compared with daytime readings, and only 18% of both AAs and Caucasians had a decrease in nocturnal DBP by 10% or more. However, 30% of AA and 9% of Caucasian donors showed “inverse dipping”
and had mean nocturnal SBP higher than mean daytime SBP.

The regression analyses incorporating all AA and Caucasian donors indicated that race had no influence on the associations between the subjects’ age at donation and their GFR, serum creatinine concentration, urine albumin excretion, or BP measurements. However, the interaction between race and age at donation on CrCl was statistically significant ($p < 0.030$). For every year older AA subjects were at time of donation, the present CrCl values were 0.6 units lower on average; however, among Caucasian subjects, for every year older at the time of donation, the present CrCl values were 2.1 units higher on average. When similar analyses were performed using current age at time since donation instead of age at donation, there were no interactions with race, indicating that race had no influence on the associations between subjects’ current age or time since donation and their GFR, CrCl, serum creatinine concentration, urine albumin excretion, or BP measurements.

Regression analyses involving only the AA donors illustrated several significant relationships. After adjusting for gender, older age at time of donation was associated ($p = 0.046$) with lower GFR values when compared with younger ages. Figure 1 illustrates this association. For every 10 years older at time of donation, current GFR values were 8.4 ml/min per 1.73 m$^2$ lower on average. Additionally, after adjusting for age at donation (or present age or time since donation), female donors had significantly lower serum creatinine concentration than male donors (adjusted mean for women $= 0.98$ versus adjusted mean for men $= 1.31$, $p < 0.0001$). No other significant associations were noted between gender and age variables with any of the renal function or BP measures. Additional analyses indicated that body mass index had no significant association with any of the renal function or BP measures.

Discussion

This study is the first to evaluate the long-term effects of uninephrectomy on kidney function and BP in AA kidney donors using measured GFR and 24-hour ambulatory BP monitoring. Our findings indicate that, when carefully selected, AAs have well preserved renal function many years after kidney donation. At the time of donation, all of our kidney donors had creatinine clearance above 100 ml/min,

### Table 3. 24-h BP measurement characteristics among study participants at time of study evaluation

<table>
<thead>
<tr>
<th></th>
<th>African Americans ($n = 33$)</th>
<th>Caucasians ($n = 11$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 24-h data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (95% CI)</td>
<td>123.2 (117.9, 128.4)</td>
<td>130.1 (120.0, 140.2)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>121.0 (114.0, 133.0)</td>
<td>131.0 (116.0, 139.0)</td>
</tr>
<tr>
<td>DBP, mean (95% CI)</td>
<td>74.5 (71.3, 77.7)</td>
<td>78.3 (74.0, 82.5)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>74.0 (68.0, 79.0)</td>
<td>77.0 (75.0, 81.0)</td>
</tr>
<tr>
<td>MAP, mean (95% CI)</td>
<td>91.3 (87.4, 95.1)</td>
<td>96.5 (90.8, 102.2)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>90.0 (82.0, 96.0)</td>
<td>98.0 (90.0, 104.0)</td>
</tr>
<tr>
<td>Daytime data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (95% CI)</td>
<td>124.1 (118.6, 129.5)</td>
<td>132.3 (122.6, 142.0)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>121.0 (115.0, 132.0)</td>
<td>132.0 (119.0, 140.0)</td>
</tr>
<tr>
<td>DBP, mean (95% CI)</td>
<td>75.6 (72.2, 79.0)</td>
<td>80.8 (76.9, 84.7)$^a$</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>76.0 (68.0, 79.0)</td>
<td>80.0 (77.0, 84.0)$^a$</td>
</tr>
<tr>
<td>MAP, mean (95% CI)</td>
<td>92.2 (88.1, 96.3)</td>
<td>98.8 (93.6, 104.0)$^a$</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>92.0 (84.0, 97.0)</td>
<td>100.0 (92.0, 105.0)$^a$</td>
</tr>
<tr>
<td>Nighttime data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (95% CI)</td>
<td>121.9 (116.5, 127.2)</td>
<td>127.5 (116.8, 138.1)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>119.0 (111.0, 126.0)</td>
<td>129.0 (111.0, 140.0)</td>
</tr>
<tr>
<td>DBP, mean (95% CI)</td>
<td>72.5 (69.2, 75.8)</td>
<td>74.8 (70.3, 79.3)</td>
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<tr>
<td>median (IQR)</td>
<td>70.0 (67.0, 77.0)</td>
<td>74.0 (70.0, 78.0)</td>
</tr>
<tr>
<td>MAP, mean (95% CI)</td>
<td>89.5 (85.6, 93.4)</td>
<td>93.1 (87.0, 99.2)</td>
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<tr>
<td>median (IQR)</td>
<td>86.0 (82.0, 94.0)</td>
<td>95.0 (84.0, 101.0)</td>
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<tr>
<td>Nighttime/daytime ratio</td>
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<td></td>
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<tr>
<td>SBP, mean (95% CI)</td>
<td>98.4 (96.4, 100.3)</td>
<td>96.2 (94.1, 98.4)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>97.5 (94.1, 101.6)</td>
<td>97.3 (95.0, 98.5)</td>
</tr>
<tr>
<td>DBP, mean (95% CI)</td>
<td>96.1 (93.8, 98.5)</td>
<td>92.5 (90.4, 94.6)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>96.2 (90.9, 100.0)</td>
<td>92.8 (92.2, 94.8)</td>
</tr>
<tr>
<td>MAP, mean (95% CI)</td>
<td>97.3 (94.9, 99.6)</td>
<td>94.1 (92.0, 96.2)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>96.2 (93.5, 101.1)</td>
<td>95.0 (91.8, 96.0)</td>
</tr>
<tr>
<td>BP dipping status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP dipper</td>
<td>2 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DBP dipper</td>
<td>6 (18)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Current HTN medication prescription</td>
<td>1 (3)</td>
<td>4 (36)$^a$</td>
</tr>
<tr>
<td>Current HTN (daytime BP $\geq$ 135/85)</td>
<td>8 (24)</td>
<td>5 (45)</td>
</tr>
</tbody>
</table>

All of the BP measurements are expressed as mmHg. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CI, confidence interval; IQR, interquartile range. $^aP < 0.05$ as compared to AA donors.
proteinuria below 250 mg/24 hours, and office BP less than 140/90 mmHg.

Extensive data regarding the long-term effects of kidney donation on kidney function in Caucasian donors have been published previously (5,10–15). In the majority of studies, however, kidney function was assessed by measuring serum creatinine concentration or creatinine clearance and not true GFR, and thus comparisons with our data are difficult to make (8). Watnick (13) found the mean GFR of 66 ml/min per 1.73 m² measured by inulin clearance in 29 donors with similar ages and intervals after donation to our Caucasian donor group. In a more recently published study from Minnesota, a subgroup of subjects had GFR measured by plasma disappearance of iothexol (16). Compared with donors in this series, our control group of Caucasian donors had higher measured GFR (78.2 ml/min versus 71.8 ml/min), although the interval from donation was very similar (12 ± 4 years for our series versus 12 ± 9 years for Minnesota donors). It is possible that higher GFR in our Caucasian donor group is due to younger age both at the time of donation (36 ± 9 yrs for our group versus 41 ± 11 years for Minnesota donors) and at the time of the study (49 ± 11 yrs for our group versus 53 ± 10 years for Minnesota donors). In addition, the measured GFR in our and their studies was performed using different methodologies. Finally, it has been suggested that iothalamate clearance may yield higher GFR values than inulin clearance and explain difference in our and Watnick’s GFR data (17,18).

In our study the mean GFRs in AA kidney donors were not different from those in CA donors matched for age, gender, and interval since donation. After a mean follow-up of 11 ± 4 years, only three (9%) of the AA kidney donors had GFR less than 60 ml/min per 1.73 m², and none had GFR below 50 ml/min per 1.73 m². Two of the three donors with GFR less than 60 ml/min per 1.73 m² had macroalbuminuria. Two were hypertensive, and one had both macroalbuminuria and HTN. In much larger series, Sebasky et al. (16) found that 14.5% of Caucasian kidney donors had GFRs between 30 and 60 ml/min per 1.73 m².

In contrast to data previously reported for Caucasian donors, we found an inverse relationship, albeit a nonsignificant one, between GFR and interval after donation in AA donors (5). Our data indicate that after donation GFR decreases by 0.38 ml/min per 1.73 m² per year. Similar to data obtained in Caucasian donors, we observed a significant trend for higher GFR values in AAs who were younger at the time of donation, again suggesting greater compensatory increase in GFR in those who remained with one kidney at a younger age. Consistent with the previous data, GFR in AA donors had a tendency (P = 0.066) to decline with increasing age. After adjusting for gender, the slope of decline of GFR with the age in our series for AA donors (−0.35 ml/min per 1.73 m² per year) was similar to that previously reported for Caucasian donors (−0.49 ml/min per 1.73 m² per year) (5).

According to the National Health and Nutritional Examination Survey (NHANES) data, 9.7% and 2.4% of the general population of AAs age 20 years or older have microalbuminuria and macroalbuminuria, respectively (19). Additionally, the prevalence of microalbuminuria and macroalbuminuria in Caucasian kidney donors after donation has been reported to be 11.5 and 1.2%, respectively (5). In our study, the prevalence of both microalbuminuria and macroalbuminuria was higher among AA donors than was previously reported in Caucasian donors and in the general AA population with two kidneys. Additionally, the prevalence of microalbuminuria in AA donors was similar to that reported by Nogueira et al. (8). Our data indicate that in AAs, a decrease in renal mass by 50% is associated with two- to four-fold increase in the prevalence of CKD (defined by pathologic albumin excretion). Although the prevalence of increased urine albumin excretion was the same in hypertensive and normotensive AA donors (28.5% versus 30.7%), the mean albumin excretion was higher in hypertensive than normotensive AA donors (231 mg/24 hours versus 104 mg/24 hours). In AA donors, age at donation and DBP were significantly associated with albuminuria (P = 0.03 and P = 0.02, respectively); however, we did not observe significant association between urine al-

Figure 1. Influence of age at time of donation on GFR. Older age at time of donation is associated (P = 0.046) with lower GFR when compared with younger ages.
albumin excretion and time interval since donation. In our Caucasian donor group, the prevalence of microalbuminuria was higher and the prevalence of macroalbuminuria was lower than reported in a recent study (5). The age and gender of our study subjects, as well as the interval since donation were similar to published data and cannot be an explanation for this discrepancy. Possible reasons may be the natural sampling variation arising from the relatively small number of Caucasian subjects or that we used 24-hour urine collection for determination of albumin excretion instead of spot urine analysis.

On the basis of NHANES data, HTN is present in 33.5% of AAs and 28.9% Caucasians (20). Furthermore, AA women are typically more likely than men to suffer from HTN (35.8% versus 30.9%). The prevalence of HTN in AA donors in our study was less than that in the AA population with two kidneys. In contrast to the general AA population, HTN was more prevalent in male than female kidney donors. Age at the study, age at donation, and the interval since donation were not different for female AA donors (43.81 ± 8.82, 32.95 ± 6.19, and 10.90 ± 5.02 years) versus male donors (40.54 ± 6.71, 29.09 ± 4.20, and 11.45 ± 5.00 years). However, hypertensive female donors were older than hypertensive male donors (51.25 ± 11.81 years versus 37 ± 3.60 years).

Self-reported prevalence of HTN in Caucasian donors was 24.7% (16). Our study indicates that HTN, although more prevalent in the AA than Caucasian general population with two kidneys, is less prevalent in AAs than Caucasians with 50% reduction in kidney mass. Despite a low prevalence of HTN, only 18% of AA donors had nocturnal dipping of SBP or DBP more than 10%. Even fewer of them (6%) had a nocturnal/daytime BP ratio <0.90. It had been suggested that a loss of nocturnal decrease in BP precedes development of microalbuminuria in patients with type 1 diabetes (21). In contrast in our study, 71% of nondippers had normal urinary albumin excretion, and we found no difference in the prevalence of nocturnal dipping between AA kidney donors with normal and abnormal urinary albumin excretion. Furthermore, although it has been suggested that nondipping status predicts decline in GFR over 3.2 years (22), in our study no difference was found in GFR between dippers and nondippers.

Two recent studies reported higher prevalence of HTN in AA donors. However, there are major methodologic differences between our study and these two reports. One of them used insurance claim data, and the other utilized only office BP measurement and estimated GFR. These data do not allow direct comparison with our observation (8,23).

Our study has important limitations. The total number of study subjects in both race groups is relatively small, and the AAs studied represent less than 50% of all AA kidney donors who could have been studied. Thus it is possible that some of our findings may be biased on the basis of subjects’ willingness/unwillingness to participate in our study. Additionally, the follow-up interval since donation was not extremely long. Furthermore, the majority of our donors were younger than 35 years, and none of them were older than 46 years at the time of donation. Currently the average age of living related AA kidney donor is 36.6 years (personal communication, Ms. Katarina Linden, United Network of Organ Sharing [UNOS]). We tried to overcome these limitations by inclusion of very precise measurements of kidney function and damage.

In conclusion, carefully selected AA kidney donors have preserved kidney function and lower prevalence of HTN than the general population of AAs. Older AA donors have lower GFR than younger donors. Of concern is that abnormal albumin excretion is more prevalent and that the vast majority of them have lost physiologic decrease in nocturnal BP. The consequences of these changes remain unclear at this time. None of our donors developed any comorbidity, but a recent report from Japan raises serious concerns if they do (24). Analyses of a current registry of kidney donors involving a much larger number of AA subjects will provide more insight into this phenomenon.

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Disclosures

None.

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