Adaptive hyperfiltration in the aging kidney after contralateral nephrectomy

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A SHORTAGE OF KIDNEYS FOR transplantation (Tx) in the United States has resulted in a recipient waiting list in excess of 50,000 and a median waiting time of 1,131 days (38). One measure adopted to lower the donor deficit has been the increasing use of unrelated, living donor transplants (35, 36, 38). Another recent source of additional donors has been donors above age 60 yr at the time of nephrectomy (57–82 yr; median 64 yr). Inspection of plots of GFR as a function of age in large samples of healthy humans reveals an inverse relationship that only becomes unambiguously obvious during the sixth decade (6, 15). We accordingly selected the middle of the sixth decade to divide our subjects into youthful and aging groups. This cut-off was selected before analysis of our data. In the youthful and all but seven members of the aging group (57–82 yr; n = 16). Inspection of plots of GFR as a function of age in large samples of healthy humans reveals an inverse relationship that only becomes unambiguously obvious during the sixth decade (6, 15). We accordingly selected the middle of the sixth decade to divide our subjects into youthful and aging groups. This cut-off was selected before analysis of our data. In the youthful and all but seven members of the aging group, the nephrectomy was performed to donate a living transplant. All living kidney donors underwent rigorous testing preoperatively, and subjects with hypertension (BP >140/90), diabetes (fasting glucose >126), proteinuria (24 urine protein >50 mg), or creatinine clearance <80 ml/min are not allowed to donate. Magnetic resonance (MR) angiograms (MRA) are routinely performed before donation, and any evidence of renal artery stenosis is a contraindication to donation. The remaining seven aging subjects were nephrectomized to remove a hypernephroma; they were included because of a dearth of Tx kidney donors in their seventh decade and beyond. The latter subjects were selected by examining the records of all patients who underwent a radical nephrectomy at our institution between 2000 and 2002. The records from patients aged

METHODS

Patient population. The subjects of our study were 32 individuals who had undergone a uninephrectomy to either donate a kidney for Tx or to remove a renal carcinoma. They were recruited 6–8 yr after nephrectomy to permit adaptive hyperfiltration to reach peak values. Using 55 yr of age as a cutoff, they were divided into a youthful group (<55 yr; n = 16) and an aging group (57–82 yr; n = 16). Inspection of plots of GFR as a function of age in large samples of healthy humans reveals an inverse relationship that only becomes unambiguously obvious during the sixth decade (6, 15). We accordingly selected the middle of the sixth decade to divide our subjects into youthful and aging groups. This cut-off was selected before analysis of our data. In the youthful and all but seven members of the aging group, the nephrectomy was performed to donate a living transplant. All living kidney donors underwent rigorous testing preoperatively, and subjects with hypertension (BP >140/90), diabetes (fasting glucose >126), proteinuria (24 urine protein >50 mg), or creatinine clearance <80 ml/min are not allowed to donate. Magnetic resonance (MR) angiograms (MRA) are routinely performed before donation, and any evidence of renal artery stenosis is a contraindication to donation. The remaining seven aging subjects were nephrectomized to remove a hypernephroma; they were included because of a dearth of Tx kidney donors in their seventh decade and beyond. The latter subjects were selected by examining the records of all patients who underwent a radical nephrectomy at our institution between 2000 and 2002. The records from patients aged

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>55 yr at the time of surgery were selected for further examination. Any patient with known preexisting kidney disease, hypertension, or diabetes was excluded from the study. Kidney disease was defined as the presence of any of the following: known, preexisting glomerular or interstitial disease; serum creatinine >1.4 mg/dl; or proteinuria as detected by urine dipstick. Hypertension was defined as a preoperative blood pressure of >140/90 or the use of any hypertensive medication. Diabetes was defined as a fasting blood glucose >126 mg/dl or a known diagnosis of diabetes, predating surgery. All subjects underwent either an MRA or computed tomographic (CT) angiography before the uninephrectomy, and those with renal artery stenosis were excluded. Seven subjects remained after the exclusion criteria were applied. Operative notes of these remaining patients were carefully reviewed for evidence of large-vessel disease. None of the subjects who participated in this study had renal artery stenosis on gross inspection or by MRA/CT. As controls we used 180 healthy volunteers aged 18–88 yr, who had served as normal controls for our laboratory over the past two decades (15). Age below or above 55 yr, respectively, was used to divide the subjects into two groups so as to provide control values for a single-kidney (SK) GFR in a healthy youthful or aging binephric population.

Physiological evaluation. All subjects underwent a determination of GFR, renal plasma flow (RPF), and preglomerular vascular pressures, according to a protocol approved by the Institutional Review Board of Stanford University School of Medicine. Initially, blood was sampled for determination of plasma oncotic pressure (πr). Urine was voided spontaneously after diuresis had been established with an oral water load (10–15 ml/kg). A priming dose of inulin (50 mg/kg) and PAH (2 mg/kg) was then administered. Thereafter, inulin and PAH were given by continuous infusion to maintain plasma levels constant at ~20 and 1.5 mg/dl, respectively.

Arterial blood pressure was determined using a dynamap at the time of admission to the general clinical research center and 60 min after the priming infusion. With rare exception, arterial blood pressure measurements did not change during the study. In the few cases where there were fluctuations, the average value was used for our analysis. Four timed urine collections were then made, each of which was bracketed by a blood sample drawn from a peripheral vein. The GFR was expressed as the average value for the four timed inulin clearances. The rate of RPF was estimated by dividing the corresponding clearance of PAH by 0.9, a value that our laboratory has validated as the mean PAH extraction ratio in individuals with normal renal function (2). The GFR and RPF for a single kidney in binephric individuals were expressed as half of the corresponding two-kidney value. Inulin and PAH concentrations were determined with colorimetric methods using a Technicon Auto Analyzer II (2). Plasma afferent oncotic pressure (πA) was measured directly using a Wescor 4400 membrane osmometer (Wescor, Logan, UT), as described by us in detail elsewhere (5). Effluent (postglomerular) oncotic pressure (πE) was calculated as follows: πE = πA/(1 – FF), where FF is the filtration fraction. The mean glomerular intracapillary oncotic pressure (πEC) was calculated as an average value of πA and πE, as described previously (5).

Calculation of whole kidney Kf. A mathematical model for the glomerular filtration of water (5, 7) was used to calculate the whole kidney Kf, which is the product of glomerular hydraulic permeability and the total filtration surface area of all glomerular capillaries, in the two kidneys of binephric controls or the single kidney of uninephric subjects. SK-Kf was derived for binephric subjects by dividing the former value by two. The input values for the model included the measured values of GFR, RPF, and πA, as well as an assumed value for the glomerular transcapillary hydraulic pressure difference (ΔP). The latter quantity cannot be directly measured in humans. However, using an indirect curve-fitting technique, we have estimated that ΔP approximates 40 mmHg in healthy binephric humans below age 55 yr (24) and assigned this value to the youthful binephric control group in the present study. To allow for the possibility of an increase in ΔP, consequent on higher arterial pressure in the aging groups (15), we then assigned the latter an assumed ΔP value of 45 mmHg. We then performed a sensitivity analysis to set limits on those changes in ΔP or computed Kf that would be necessary to explain the observed level of hyperfiltration in the uninephrectomized experimental population.

Statistical analysis. All data with a Gaussian distribution are expressed as means ± SD. Those with a non-Gaussian distribution are expressed as the median value and range. Statistical significance between groups was defined at P < 0.05. Statistical calculations were performed using the S-PLUS 2000 software program (version 2, Insightful, Seattle, WA). Continuous variables were compared by one-way ANOVA for parametric data and the Kruskal-Wallis test for nonparametric data. A two-way ANOVA was used to determine whether there was a statistically significant interaction between age and nephric states. Unpaired t-tests were then used to compare group means, adjusted for multiple comparisons by the Bonferroni method. Categorical variables were examined using a simple χ2 analysis of Fisher’s exact test when the number of data elements was small. Linear regression analysis was used to derive slopes of GFR or vs. age for binephric and uninephric subjects. The standard assumptions for linear regression were met. A Student’s t-test was used to determine the significance of the difference between the slopes in the binephric and uninephric groups of the GFR vs. age plot.

RESULTS

Magnitude of adaptive hyperfiltration. The difference in SK-GFR between binephric and uninephric groups and between the youthful and aging groups is illustrated in Fig. 1 and summarized in Table 1. A two-way ANOVA by age category and the number of kidneys showed no statistically significant interaction effect (P > 0.05); therefore, age category and number of kidneys independently contributed to the mean values. On average, SK-GFR in youthful uninephric subjects exceeded that in youthful binephric controls, 74 ± 17 vs. 52 ± 8 ml·min⁻¹·1.73 m⁻², respectively, reflecting an increment in the former of 42%. The corresponding excess in aging subjects was 58 ± 13 vs. 42 ± 9 ml·min⁻¹·1.73 m⁻² in uninephric vs. binephric subjects, respectively, an increment of 38%. The latter increment is not significantly different from that observed in the youthful group. That the capacity for adaptive hyperfil-
Table 1. Study subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Binephric (n = 143)</th>
<th>Uninephric (n = 16)</th>
<th>Binephric (n = 37)</th>
<th>Uninephric (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr [means ± SD (range)]</td>
<td>31±9 (18–54)</td>
<td>35±7 (21–48)</td>
<td>65±9 (55–88)</td>
<td>66±8 (56–81)</td>
</tr>
<tr>
<td>1-Kidney GFR, ml·min⁻¹·1.73 m⁻²</td>
<td>52±8</td>
<td>74±17*</td>
<td>42±9*</td>
<td>58±13†</td>
</tr>
<tr>
<td>1-Kidney RPF, ml·min⁻¹·1.73 m⁻²</td>
<td>282±63</td>
<td>388±86*</td>
<td>210±54*</td>
<td>282±72†</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.19±0.04</td>
<td>0.19±0.02</td>
<td>0.20±0.04</td>
<td>0.21±0.03</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>89±9</td>
<td>82±8*</td>
<td>96±8*</td>
<td>96±10†</td>
</tr>
<tr>
<td>πA, mmHg</td>
<td>24.9±2.6</td>
<td>27.7±1.8*</td>
<td>25.1±2.3</td>
<td>26.1±2.2</td>
</tr>
<tr>
<td>πGc, mmHg</td>
<td>27.8±2.6</td>
<td>31.0±2.2*</td>
<td>28.3±3.0</td>
<td>29.5±2.1</td>
</tr>
<tr>
<td>Urinary albumin/creatinine, median (range)</td>
<td>4.4 (1.9–11.0)</td>
<td>5.9 (1.9–37.6)</td>
<td>10.5 (2.4–22.2)</td>
<td>10.7 (2.0–83.6)</td>
</tr>
<tr>
<td>1-Kidney Kf, ml·min⁻¹·mmHg⁻¹ [median (range)]</td>
<td>4.8 (2.4–21.4)</td>
<td>10.1 (6.4–30.7)*</td>
<td>2.8 (1.6–9.0)*</td>
<td>4.5 (2.5–8.1)‡‡</td>
</tr>
<tr>
<td>ΔP, mmHg</td>
<td>40</td>
<td>45</td>
<td></td>
<td></td>
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</tbody>
</table>

GFR, glomerular filtration rate; RPF, renal plasma flow; MAP, mean arterial pressure; πA, plasma afferent oncocentric pressure; πGc, glomerular intracapillary oncotic pressure; Kf, ultrafiltration coefficient; ΔP, glomerular transcapillary hydraulic pressure difference. *P < 0.05 vs. youthful binephric. †P < 0.05 vs. youthful uninephric. ‡P < 0.05 vs. aged binephric.

Adaptive hyperfiltration and aging

In uninephric subjects, albuminuria increased with age, suggesting that there has been reported in a subset of kidney donors previously (9).

**Determinants of adaptive hyperfiltration.** The mean SK-RPF in uninephric subjects exceeded that in binephric controls by 38% in youthful subjects 388 vs. 282 ± 63 ml·min⁻¹·1.73 m⁻², respectively (P < 0.05). Mean elevation of similar magnitude (34%) was observed in aging vs. youthful subjects: 282 ± 72 vs. 210 ± 54 ml·min⁻¹·1.73 m⁻², respectively (P < 0.05). That the increase in RPF in both aging and youthful subjects postnephrectomy was proportional to the corresponding increase in GFR is reflected by the similar filtration fraction in both binephric and uninephric subjects within each age group (Table 1).

Mean πA was 2.8 mmHg higher in youthful uninephric (P < 0.05) and 1.0 mmHg higher in aging uninephric subjects (P = not significant) than in binephric controls of corresponding age (Table 1). From πA and the filtration fraction we estimated the corresponding value for mean πGc (5). The excess in youthful uninephric subjects was 3.2 mmHg, to 31.0 ± 2.2 mmHg. The corresponding excess in aging uninephric subjects was 1.2 mmHg, to 29.5 ± 2.1 mmHg (P = not significant; Table 1). Since πGc is the force opposing the formation of filtrate, the higher value postnephrectomy should lower and not elevate the GFR. By exclusion, increases in ΔP and/or Kf, the remaining determinants of GFR (7), must be invoked to explain postnephrectomy hyperfiltration. Mean arterial pressure was higher on average by 7 mmHg in aging vs. youthful binephric controls (P < 0.05; Table 1). Transmission of some fraction of this excess into glomerular capillaries provides the basis for a higher “best guess” value for ΔP in the aging than youthful binephric subjects, namely, 45 and 40 mmHg, respectively (7).

We compared SK-Kf using the best guess ΔP values stipulated above. The median value was significantly lower in aging than in youthful binephric controls, 2.8 (1.6–9.0 ml·min⁻¹·mmHg⁻¹) vs. 4.8 (2.4–21.4 ml·min⁻¹·mmHg⁻¹), respectively (Fig. 3). To compute the isolated increase in Kf that would be required to account for the observed level of hyperfiltration in uninephric subjects, we held the aforementioned values of ΔP constant at the assumed binephric values. Our model reveals that the median SK-Kf in youthful uninephric subjects would have to increase about twofold to 10.1 ml·min⁻¹·mmHg⁻¹ to account for the observed hyperfiltration.

![Fig. 2. Single-kidney GFR vs. age in uninephrectomized (▲) vs. control binephric subjects (○).](http://ajprenal.physiology.org)
tion, given the levels of RPF and $\pi_A$ listed in Table 1 (Fig. 3). The corresponding isolated increase in median SK-$K_f$ required to explain the observed hyperfiltration in aging uninephric subjects is 61%, to 4.5 ml·min$^{-1}$·mmHg$^{-1}$ (Fig. 4).

We next held the values for $K_f$ in each uninephric category constant at the levels listed for the binephric condition in Table 1 and calculated the extent of an isolated increase in $\Delta P$ that would be necessary to account for the observed GFR. To do this, we increased $\Delta P$ above the assigned values at 1-mmHg increments until we restored $K_f$ to the binephric value. This revealed that an isolated 7 mmHg in $\Delta P$ to 47 mmHg in the youthful uninephric group, and a 5 mmHg increase in the $\Delta P$ to 50 mmHg in aging uninephric subjects can account for the observed hyperfiltration. An increase in $\Delta P$ of this magnitude in aging but not youthful uninephric subjects is consistent with the large observed difference of 14 mmHg in mean arterial pressure, respectively, 96 ± 10 vs. 82 ± 8 mmHg (Table 1).

We interpret our computations to indicate that adaptive hyperfiltration after contralateral uninephrectomy in youthful and aging subjects is a consequence of either an isolated doubling of SK-$K_f$ or a respective isolated increase by 7 or 5 mmHg in $\Delta P$, or a combination of smaller increments of both SK-$K_f$ and $\Delta P$.

DISCUSSION

Researchers have long been interested in the compensatory renal response that follows contralateral nephrectomy. Investigators in the first half of the 20th century undertook animal studies to examine the physiological responses to uninephrectomy. Shortly thereafter, kidney transplantation provided a unique opportunity to study the effects of uninephrectomy in the healthy living kidney of humans following contralateral nephrectomy for kidney donation. This study confirmed previous experimental observations that, after nephrectomy, the donor’s GFR exceeded 50% of the prenephrectomy SK value (4). Numerous investigators have since replicated these findings (3, 10–12, 19, 29–31, 34, 39, 40), but few have evaluated the compensatory response of the aging kidney after nephrectomy (10, 40). The aging group in the present study ranged in age from 57 to 81 yr, with an average age of 67 yr. The average extent of adaptive hyperfiltration was 38%, representing an increase in mean SK-GFR from 41 to 59 ml/min. Thus we have demonstrated that in healthy subjects aged >55 yr, adaptive hyperfiltration is preserved and that the magnitude of such hyperfiltration is similar to or only slightly smaller than corresponding values in youthful subjects.

Our study also reveals that GFR in uninephric subjects exhibits a negative correlation with advancing age (Fig. 2), as has long been known to be the case in healthy binephric subjects (15). We have recently reported that the latter phenomenon can be attributed to a decline in $K_f$ (15). This loss of intrinsic, ultrafiltration capacity by aging kidneys in turn results from a reduction in the absolute number of glomeruli (28), a 10–40% prevalence of global glomerulosclerosis (17, 18) and a decline in both filtration surface density and hydraulic permeability in surviving patent glomeruli (15). The present study reveals that notwithstanding the declining GFR and impairment of filtration capacity that accompany advancing age, individuals between 55 and 80 yr of age can elevate their GFR substantially after uninephrectomy (Fig. 1). Our theoretical analysis of glomerular pressure and flows indicates that one potential determinant of such hyperfiltration is an isolated enhancement of $K_f$ by 61%, on average.

The $K_f$ is, of course, the product of hydraulic permeability and filtration surface area. It is difficult to envisage how the structures in the glomerular capillary wall that determine per-
meability, namely, endothelial fenestrae, the basement membrane, and the filtration slit diaphragms, could change in response to uninephrectomy (8). On the other hand, it is highly probable that glomeruli participated in the compensatory hypertrophy that occurs in the wake of nephrectomy (10), thereby enhancing filtration surface area. Whereas it is conceivable that a glomerular hypertrophic response could account for the potential doubling of $K_f$ observed in our youthful uninephric subjects, there are reasons to suspect that the corresponding hypertrophic response in aging uninephric subjects could be blunted, precluding an isolated, 61% increase in $K_f$ needed to account for the observed level of hyperfiltration in this circumstance (Fig. 3). Autopsy studies of subjects not known to have a renal disease have repeatedly demonstrated a reduction in renal weight and volume by about one-third, between the fifth and ninth decades (20). As suggested by a pattern of cortical ischemia (16), such loss of renal mass is predominantly from the outer cortex. A loss of vascular, and especially capillary, mass has been held to result in glomerular tuft collapse, with a reduction in the number of vascular channels and, eventually, hyalination of the tuft (23). The pathological hallmarks of this obliterative microvasculopathy of aging are a high prevalence of glomerulosclerosis that is far more prevalent in the outer cortex than in deeper layers and the juxtamedullary cortex (17, 18, 21, 23). Increasing global glomerulosclerosis and age are, in turn, related linearly to both volume of interstitium (17) and to intrarenal arterial pathology, particularly the fractional wall and (inversely) the fractional luminal area of arteries and arterioles (18). We submit that the microvascular alteration and atrophic renal cortex of the aging kidney could limit any hypertrophic response to contralateral nephrectomy. In keeping with this possibility are the observations of Edgren et al. (10) that uninephrectomy in older donors reduced glomerular hypertrophy (1), a response to initial nephrectomy, and focal and segmental glomerulosclerosis (27), a hallmark of the remnant kidney phenomenon. Progressive azotemia in 6 of the 21 patients progressed to end-stage renal failure in 2 instances. Age, increasing proteinuria, and the aforementioned glomerulomegaly and focal segmental glomerulosclerosis were identified as risk factors for progression (27). The fact that >50% of renal mass was removed (uni + partial nephrectomy) distinguishes these subjects from transplant donors, in whom only 50% of renal mass is removed. Given the striking variability in the number of glomeruli in the human kidney (28), however, it could be that those aging subjects in the lowest part of the range would be left with few enough glomeruli after uninephrectomy to promote the remnant kidney phenomenon.

As stated previously, autopsy studies have demonstrated that among subjects >60 yr of age, the percentage of glomeruli that are globally sclerosed is frequently in the 10–40% range (17, 18), leading to a state of functional glomerulopenia. In addition, Nyengaard and Bendsten (28) demonstrated that there is also absolute glomerulopenia in the aging kidney, presumably as a consequence of complete resorption of obsolescent, sclerosed glomeruli. They used a direct and unbiased stereological method (the fractionator) to measure the number and size of glomeruli of subjects coming to autopsy, who were known to have normal kidney function and shown to have otherwise normal renal structure (28). Subjects over 55 yr of age had fewer glomeruli per kidney than those below 55 yr old: 560 ($\pm\text{SD} = 112 \times 10^3$ vs. 695 ($\pm\text{SD} = 137 \times 10^3$), respectively ($P < 0.001$). Thus glomerulopenia, whether manifested as global sclerosis or resorption of sclerotic glomeruli, is strongly associated with the observed GFR reduction of advancing age. For example, aging subjects who are 1 SD below the mean would have only 448,000 glomeruli. Assuming even a modest 10% prevalence of global sclerosis, the number of filtering glomeruli would approximate only 400,000. This means that aging subjects >1 SD below the mean would have <30% of the average number of 1,400,000 glomeruli found in binephric youthful individuals. We suspect that functional glomerulopenia of this magnitude could be sufficient to evoke the remnant kidney phenomenon. This could be especially dangerous in aging individuals who are prone to superimposition of the renovascularopathies associated with the development of hypertension (13) or bilateral renal artery stenosis (32, 37, 41), two common causes of end-stage renal failure in the elderly.

We submit that some members of our aging uninephric group in the lowest GFR quartile (37–50 ml/min; Fig. 1) could have sufficiently marked glomerulopenia to develop the remnant kidney phenomenon. Given current expectations of lon-

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We submit that some members of our aging uninephric group in the lowest GFR quartile (37–50 ml/min; Fig. 1) could have sufficiently marked glomerulopenia to develop the remnant kidney phenomenon. Given current expectations of lon-
gevity into the ninth decade and beyond, this could progress to end-stage renal failure before the end of their natural lifespan. The decision to donate a kidney from an aging individual for Tx is further confounded by a high risk-to-benefit ratio, given the abbreviated survival of allografts from aging donors (38). We propose that a longitudinal study of aging individuals undergoing nephrectomy should be undertaken to elucidate the incidence, characteristics and predictors of progressive renal failure. Such information could then be used to develop exclusion criteria for potential living donors who are aging.

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REFERENCES


