Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass

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Deen, William M., David A. Maddox, Channing R. Robertson, and Barry M. Brenner. Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass. Am. J. Physiol. 227(3): 556-562. 1974.—The mechanisms responsible for the adaptive increase in glomerular filtration rate (GFR) following unilateral nephrectomy were studied in mutant Wistar rats having accessible surface glomeruli. Pressures and flows were measured in single glomeruli of the left kidney 2-4 wk after right nephrectomy and in a normal hydropenic control group. Following uninephrectomy, whole-kidney GFR and kidney weight increased in proportion (by about 40%); these increases were accompanied by uniform increases in superficial cortical single-nephron (SN) GFR and glomerular plasma flow (GPF). As in control rats, filtration pressure equilibrium was observed after uninephrectomy. Mean transcapillary hydraulic pressure difference (ΔP) increased from 34 to 40 mmHg. The ultrafiltration coefficient (Kf), the product of effective hydraulic permeability and capillary surface area, was determined in uninephrectomized rats under conditions designed to prevent the achievement of filtration pressure equilibrium (2% plasma loading). KE was found to be identical, on the average, to the value recently reported for rats with intact kidneys (0.078 nl/(s cm² mmHg)). The findings suggest that the adaptive increase in SNGFR following uninephrectomy results primarily from increases in GPF and (ΔP), with the increase in GPF accounting for approximately three-fourths of the increase in SNGFR.

GLOSSARY OF SYMBOLS

(angular parentheses) mean value
(ΔP) mean renal arterial pressure, mmHg
C protein concentration, g/100 ml
FAFR, efferent arteriole blood flow and plasma flow, respectively, nl/min
EAPF initial glomerular blood flow and plasma flow, respectively, nl/min
GFR blood hemocrit in femoral artery or efferent arteriole
Hct A effective hydraulic permeability, nl/(s mmHg cm²)
Kf ultrafiltration coefficient, nl/(s mmHg)
P hydraulic pressure, mmHg
P UF net ultrafiltration pressure, mmHg
ΔP transmucosal hydraulic pressure difference, P UF - P T, mmHg
π colloid osmotic pressure, mmHg
Δπ transmucosal osmotic pressure difference, ω UF - ω T, mmHg
R resistance to blood flow, dyn s cm⁻⁵
R TA total arteriolar resistance, R A + R T, dyn s cm⁻⁵
S surface area available for ultrafiltration, cm²
SNFF single-nephron filtration fraction
SNGFR single-nephron glomerular filtration rate, nl/min
(TF/P) In tubule fluid-to-plasma inulin concentration ratio
V TF tubule fluid flow rate, nl/min

Subscripts
A afferent arteriole
C peritubular capillary
efferent arteriole
GC glomerular capillary
T proximal tubule

REDUCTION IN FUNCTIONAL RENAL MASS, whether the result of disease or surgical excision, generally leads to an adaptive increase in the rate of glomerular ultrafiltration in surviving nephrons (1, 3, 4, 18-20, 23, 26, 29). The mechanisms responsible for this adjustment in ultrafiltration have yet to be defined, owing, at least in large part, to the fact that glomeruli are rarely encountered as surface structures in the mammalian kidney and are, therefore, inaccessible to direct study in vivo. This restriction has been overcome, however, in that a unique strain of Wistar rats endowed with surface glomeruli has recently been discovered in the laboratory of Dr. Klaus Thurau, Physiological Institute, Munich, Germany. Using these rats, and appropriate techniques for determining the glomerular transcapillary driving forces for ultrafiltration, we have found it possible to gain appreciable insight into the mechanisms governing ultrafiltration under a variety of physiological and pathophysiologic conditions (8, 10, 12, 15, 24). In like manner, the present study was undertaken to define the mechanisms governing the adaptive increase in glomerular filtration rate of residual nephrons following reduction in total renal mass by unilateral nephrectomy.
METHODS

General

Eighteen adult Wistar rats weighing 243–388 g were studied. In the experimental group of 10 rats, right nephrectomy was performed under ether anesthesia 16–29 days prior to micropuncture study. Eight littermates (hence matched to the experimental group for age and weight) which were not subjected to uninephrectomy served as the control group. All rats were allowed free access to water and a standard rat pellet diet until the morning of study. Control and experimental rats were anesthetized with Inactin (100 mg/kg) and prepared for micropuncture as described previously (6, 7, 9). Sixty minutes before micropuncture the rats received an intravenous infusion of isotonic NaCl at the rate of 0.02 ml/min. Inulin was present in a concentration of 10%, thereby resulting in final plasma concentration of about 100 mg/100 ml. Mean femoral arterial pressure (AP) was monitored by means of an electronic transducer (model P23AA, Statham Instruments, Inc., Oxnard, Calif.) connected to a direct-writing recorder (model 7702B, Hewlett-Packard Co., Palo Alto, Calif.). Late surface convolutions of proximal tubules were identified as described previously (6, 7, 9). After this 60-min equilibration period, exactly timed (1–2 min) samples of fluid were collected from these tubule sites for determination of flow rate and inulin concentration and calculation of single-nephron glomerular filtration rate. The rate of fluid collection was adjusted to maintain a column of polymer oil (Kel-F polymer oil, 3M Co., Medical Products Division, St. Paul, Minn.), three to four tubule diameters in length, in a relatively constant position just distal to the site of puncture. With the use of the collection technique of controlled suction recently validated for this laboratory (5), minimal changes in tubule diameter or the position of the distal oil block were produced. Coincident with these tubule fluid collections, femoral arterial blood samples were obtained for determinations of hematocrit and plasma inulin concentration. Hydraulics pressures were measured in single capillaries within surface glomeruli with continuous-recording, servo-nulling, micropipette transducer techniques (9, 16, 30). Micropipettes with outer tip diameters of 2–3 μm and containing 1.0 M NaCl were used. Penetration of Bowman’s capsule and entry into capillaries was performed under stereomicroscopic control. Hydraulic output from the servo system was channeled via a transducer (Statham Instruments, Inc., P23Db) to a second channel of the recorder. Accuracy, frequency response, and stability features of this servo system have been described in detail elsewhere (9). In addition to direct measurements of glomerular capillary hydraulic pressure (Pgc) and proximal tubule pressure (Pp), pressures also were recorded in efferent arterioles (Ppe) and second- and third-order branch peritubular capillaries (Pce) in each rat.

To obtain estimates of colloid osmotic pressure of plasma entering and leaving glomerular capillaries, protein concentrations in femoral arterial and efferent arteriolar blood plasmas were measured as described previously (6). Colloid osmotic pressures were calculated from the equation for colloid osmotic pressure of plasma derived by Landis and Pappenheimer (21) and recently validated for the rat (11).

Colloid osmotic pressure calculated for femoral arterial plasma is taken as representative of Π for the afferent arteriole (Πa). These estimates of pre- and postglomerular protein concentration permit calculation of single-nephron filtration fraction (SNFF) and initial glomerular plasma flow rate (see equations below). From direct measurements of the decline in pressure along single afferent and efferent arterioles, and from estimates of blood flow through these vessels, vascular resistances to blood flow through these individual vessels were calculated (see equations 7–9). Coincident with these micropuncture measurements, whole-kidney clearances of inulin were performed on most rats.

Following completion of the above-described measurements under hydropenic conditions, eight rats in the experimental group underwent isoncotic plasma volume expansion, a maneuver performed to induce filtration pressure disequilibrium, which is a necessary condition for determination of the ultrafiltration coefficient. In these rats, homologous rat plasma (obtained by arterial exsanguination of a littermate on the morning of study) equal in volume to 2% body wt was infused intravenously in a 90-min period. After infusion, measurements of the above-described pressures, flows, and resistances were repeated in a period of 60 min. Separate, rather than the previously punctured, tubules, capillaries, and efferent arterioles were studied in this period. Plasma volume expansion was not performed in control rats.

Analytical. The volume of tubule fluid collected from individual nephrons was estimated from the length of the fluid column in a constant-bore capillary tube of known internal diameter. The concentration of inulin in tubule fluid was measured, usually in duplicate, by the microfluorescence method of Vurek and Pegram (28). Inulin concentration in plasma was determined by the macrofluorimetric method of Führ, Kaczmarczyk, and Krüttgen (17). Protein concentrations in efferent arteriolar and femoral arterial blood plasmas were determined, usually in duplicate, with an ultramicrocolorimeter using a recently described (6) microadaptation of the method of Lowry et al. (22).

Calculations. Single-nephron glomerular filtration rate:

\[ \text{SNGFR} = \frac{(\text{TF/P})_t \cdot \text{V}_t}{\text{SNFF}} \]  (1)

Single-nephron filtration fraction:

\[ \text{SNFF} = 1 - \frac{C_A}{C_E} \]  (2)

where \( C_A \) and \( C_E \) denote afferent and efferent arteriolar protein concentrations, respectively.

The initial plasma flow rate per glomerulus:

\[ \text{GPF} = \frac{\text{SNGFR}}{\text{SNFF}} \]  (3)

The initial blood flow rate per glomerulus:

\[ \text{GBF} = \frac{\text{GPF} \cdot \frac{1}{1 + \frac{1}{\text{Hct}_A}}}{\text{Hct}_A} \]  (4)

where \( \text{Hct}_A \), the hematocrit of afferent arteriole blood, is taken as equal to the hematocrit value for femoral arterial blood.
Plasma flow per efferent arteriole:
\[ \text{EAPF} = \text{GPF} - \text{SNGFR} \quad (5) \]

Blood flow rate per efferent arteriole:
\[ \text{EABF} = \text{GBF} - \text{SNGFR} \quad (6) \]

Resistance per single afferent arteriole:
\[ R_A = \frac{(\text{AP}) - (\text{PGC})}{\text{EABF}} \times (7.962 \times 10^{10}) \quad (7) \]

where the factor $7.962 \times 10^{10}$ is used to give resistance in dynes·seconds·centimeters$^{-5}$ when (AP) and (PGC) are expressed in millimeters Hg and GBF, in nanoliters per minute.

Resistance per single efferent arteriole:
\[ R_E = \frac{(\text{PGC}) - (\text{PC})}{\text{EAPF}} \times (7.962 \times 10^{10}) \quad (8) \]

Total arteriolar resistance for a single pre- to post-glomerular vascular unit:
\[ R_{TA} = R_A + R_E \quad (9) \]

Estimates of the net ultrafiltration pressure at the most afferent and most efferent portions of the glomerular capillary:
\[ \begin{align*}
\text{P}_{UFT} &= (\text{PGC}) - (\text{PT}) - \pi_A \quad (10) \\
\text{P}_{UFE} &= (\text{PGC}) - (\text{PT}) - \pi_E \quad (11)
\end{align*} \]

where \( \pi_A \) and \( \pi_E \), afferent and efferent arteriolar colloid osmotic pressures, respectively, were calculated from femoral arterial and efferent arteriolar plasma protein concentrations with the Landis-Pappenheimer equation \((21)\). Equations \((10)\) and \((11)\) contain the assumption that the colloid osmotic pressure of fluid in Bowman’s space \( (\pi_T) \) is negligible. This assumption has been validated by the finding for three rats in each group that the protein concentration of this fluid is less than 200 mg/100 ml. Accordingly, \( \pi_T \) is less than 0.5 mmHg.

Mean net glomerular transcapillary hydraulic pressure:
\[ (\text{AP}) = (\text{PGC}) - (\text{PT}) \quad (19) \]

The glomerular capillary ultrafiltration coefficient \( (K_f) \) is calculated using a differential equation which gives the rate of change of protein concentration with distance along the capillary. This equation, together with its derivation and the method for its solution, is given in detail elsewhere \((13,19)\).

RESULTS

Uninephrectomy vs. control data during hydropenic conditions. The measured determinants of glomerular ultrafiltration in control and uninephrectomized rats during hydropenic conditions are summarized in Tables 1 and 2, respectively, along with other pertinent whole-kidney and single-nephron data. Despite comparable values for body weight between groups, left kidney weight \( (\text{KW}) \) increased in the 16- to 29-day period postnephrectomy from a mean value \( (\text{assumed equal to that of the excised right kidney}) \) nearly identical to that of control rats \( (1.01 \text{ vs. } 0.96 \text{g}) \) to a final value of \( 1.42 \text{g}, \) a mean change from initial of \( 43 \% \pm 5 \text{ SE} \) \( (P < .001) \). This increase in left kidney weight was associated with a proportional increase in whole-kidney GFR, mean values for GFR per gram kidney weight in control and uninephrectomized rats being identical \( (0.98 \pm .02 \text{ and } 0.98 \pm .04 \text{ ml/min/g per g} \) \( \text{KW}, \) respectively). \( (\text{AP}) \) values were not different between groups. Values for SNGFR were uniformly higher in experimental vs. control rats, averaging 45.6 and 24.9 nl/min, respectively \( (P < .001) \) for SNFF were essentially the same in both groups, it follows from equation \((3)\) that the higher values for SNGFR in uninephrectomized rats were accompanied by proportionately higher values for GPF as well \( (\text{Tables} \ 1 \text{ and } 2) \). Glomerular capillary hydraulic pressures \( ^{1} \) tended to be slightly higher (and, on the

\( ^{1} \) The use of this equation assumes the axial variation in \( \text{PoC} \) to be negligible. The justification for this assumption is discussed elsewhere \((10)\).

### TABLE 1. A summary of measured determinants of glomerular ultrafiltration in control rats

<table>
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<tr>
<th>Animal No.</th>
<th>Body Wt.</th>
<th>Left Kidney Wt.</th>
<th>Right Kidney Wt.</th>
<th>(AP)</th>
<th>AT</th>
<th>TR</th>
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<td>5.3</td>
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<td>29.2</td>
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For definitions of abbreviations see Glossary and text.
TABLE 2. A summary of measured determinants of glomerular ultrafiltration in uninephrectomized rats

| Animal No. | Days Postnephrectomy | Body Wt | Final | Whole-Kidney GFR (AP) | (P/OC) | PT | CA | Cg | T1 | TE | SNGFR | SNFF | GPF | (AP) | (P/OC) | PT | CA | Cg | T1 | TE | SNGFR | SNFF | GPF |
|------------|----------------------|---------|-------|-----------------------|--------|----|----|----|----|----|--------|-------|-----|-----|-------|--------|----|----|----|----|----|--------|-------|-----|-----|
| 3          | 0.95                 | 1.50    | 1.82  | 130                   | 43     | 12 | 6.4| 9.2| 44.5| .38 | 117    | 100   | 63  | 18  | 6.4  | 22.4   | 47.6|      |     |     |     |        |       |     |
| 10         | 0.01                 | 0.48    | 1.22  | 120                   | 48     | 12 | 6.4| 9.4| 22.4| 41.7| 120    | 57    | 13  | 7.2 | 26.8  | 42.9   | 77.0| 25   | 308 |
| 11         | 0.01                 | 0.48    | 1.22  | 120                   | 48     | 12 | 6.4| 9.4| 22.4| 41.7| 120    | 57    | 13  | 7.2 | 26.8  | 42.9   | 77.0| 25   | 308 |
| 12         | 0.01                 | 0.48    | 1.22  | 120                   | 48     | 12 | 6.4| 9.4| 22.4| 41.7| 120    | 57    | 13  | 7.2 | 26.8  | 42.9   | 77.0| 25   | 308 |

For definitions of abbreviations see GLOSSARY and text. * Days postnephrectomy. † Calculated from mean values for control and uninephrectomized rats (hydropenic period) using an unpaired t test. ‡ Calculated from paired changes between plasma load and hydropenic periods in uninephrectomized rats using a paired t test.

Note: The image contains a table with data related to measured determinants of glomerular ultrafiltration in uninephrectomized rats, including columns for animal number, days postnephrectomy, body weight, kidney weight, whole-kidney GFR, plasma values, SNGFR, SNFF, GPF, and other related measurements. The table is formatted with specific values and units, and includes notes on statistical calculations and references to the GLOSSARY.
average, statistically different) in uninephrectomized rats than in controls; the mean value for the latter group was essentially identical to that reported by us previously for similarly normal hydropenic rats (8, 10, 12, 24). Values for \( P_T \) measured at random sites along surface proximal convolutions were not different between groups (Tables 1 and 2), nor were differences noted for values of \( P_C \) (control = 9 ± 0.2 vs. 10 ± 0.4 mmHg for uninephrectomized rats, \( P > .5 \)) or \( P_E \) (15 ± 0.5 vs. 15 ± 0.8, \( P > .5 \)). The hydraulic pressure drop along surface afferent arterioles ((\( \Delta P \)) - \( P_{AC} \)) was similar in control and experimental groups, averaging 72 ± 2 and 69 ± 5 mmHg, respectively. These values were uniformly and significantly higher than the pressure drop along surface efferent arterioles \( (P_{EC}) - P_E \), which averaged 37 ± 1 mmHg for controls and 42 ± 1 for uninephrectomized rats. Mean values for \( R_A \) and \( R_E \) were uniformly lower in experimental rats, averaging 2.0 ± 0.2 × 10^{-10} dyn·s·cm^{-4}, compared to a value of 3.7 ± 0.3 (\( P < .001 \)) for normal rats; the latter is in close agreement with values for normal rats reported previously (10, 12, 24).

For these eight rats, \( \frac{R_E}{(\Delta P)} \) (i.e., \( \frac{R_E}{(P_{AC}) - P_E} \)) averaged 0.99 ± 0.03. This equality between \( R_E \) and \( (\Delta P) \) indicates that filtration pressure equilibrium was achieved. For all eight rats, \( R_A \) was likewise lower in uninephrectomized rats, averaging 1.6 ± 0.2 × 10^{-10} dyn·s·cm^{-4} vs. 2.2 ± 0.2 for controls (\( P < .05 \)); the latter value again corresponds closely to that reported previously for normal hydropenia (10, 12, 24).

Despite these differences in the absolute values of \( R_A \) and \( R_E \), the filtration pressure drop \( (\Delta P) \) averaged 7.4 ± 2 mmHg (difference from zero, \( P < .05 \)) and 0.82 ± 0.06, respectively. For the six rats studied, plasma loading achieved its desired effect in that filtration pressure equilibrium was prevented. For all eight rats, \( P_{UFK} \) and \( \frac{P_{UFK}}{(\Delta P)} \) averaged 7.4 ± 2 mmHg (difference from zero, \( P < .05 \)) and 0.82 ± 0.06, respectively. For the six rats not at filtration pressure equilibrium, \( K_f \) was calculated to be 0.078 ± 0.012 ml/(s·mmHg), a value identical to that reported previously for nonnephrectomized rats under similar disequilibrium conditions (15).

### DISCUSSION

The results obtained in the present study permit examination of the mechanisms responsible for the adaptive increase in SNGFR after uninephrectomy. The rate of glomerular ultrafiltration may be expressed as

\[
\text{SNGFR} = K_f \cdot (P_{UF}) = k \cdot S \cdot (P_{UF}) \quad (13)
\]

where \( P_{UF} \) is the mean ultrafiltration pressure (\( P_{UF} \) averaged along the length of the capillary), and \( K_f \), the ultrafiltration coefficient, is the product of the effective hydraulic permeability \( k \) and total surface area \( S \) of the glomerular capillaries. It may be seen from equation 13 that the increase in SNGFR following uninephrectomy could have resulted from an increase in \( K_f \), \( (P_{UF}) \), or both. The first of these possibilities, an increase in \( K_f \), was examined by creating an experimental situation in which \( K_f \) could be determined in uninephrectomized rats. The necessary condi-

<table>
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<th>Condition</th>
<th>SNGFR (Obs)</th>
<th>SNGFR (Calcd.)</th>
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<tr>
<td>Normal hydropenia</td>
<td>24.9 ± 1.1</td>
<td>24.9</td>
</tr>
<tr>
<td>Unilateral nephrectomy</td>
<td>45.6 ± 3.1</td>
<td>46.2</td>
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</table>

Values are means ± SE. SNGFR, single-nephron glomerular filtration rate. Obs, observed; calcd, calculated. \( k_f \) = 0.078 ml/(s·mmHg).
tion of filtration pressure disequilibrium was achieved by 2% plasma loading, which permitted calculation of \( K_f \) as described previously (13, 15). \( K_f \) averaged 0.078 nl/(s · mmHg), a value remarkably similar to that reported previously for nonnephrectomized rats (15). For reasons discussed in detail elsewhere (13, 15), the existence of filtration pressure disequilibrium precludes determination of a unique value of \( K_f \) for normal hydropenic rats and uninephrectomized rats under hydropenic conditions. It was confirmed, however, with use of a recently reported model of glomerular ultrafiltration (13), that the value of \( K_f \) (0.078 nl/(s · mmHg)) determined for uninephrectomized, plasma-loaded rats at disequilibrium is also consistent with the equilibrium data obtained in this study. Since this estimate of \( K_f \) was obtained in only six rats, the possibility exists that modest changes in \( K_f \) may have occurred. To the extent that the average value of \( K_f \) determined in the present study is identical, however, to that reported previously (15) for nonnephrectomized rats, the present evidence suggests that the adaptive increase in SNGFR following uninephrectomy is the result primarily of an increase in \( P_{up} \).

As discussed in considerable detail elsewhere (13, 14), for constant \( K_f \), changes in \( P_{up} \) and SNGFR are determined solely by changes in \( C_a \), \( \Delta P \), and GPF. Changes in GPF serve to modify the average transmembrane oncotic pressure difference: increases in the former tend to reduce this pressure difference while the opposite is true for decreases in GPF. In the present study, uninephrectomy (in hydropenia) was associated with no difference in \( C_a \) relative to nonnephrectomized controls. In contrast, \( \Delta P \) and GPF were significantly larger in nephrectomized rats, averaging 40 vs. 34 mmHg and 136 vs. 76 nl/min, respectively. The observed increase in SNGFR was therefore the result of these changes in \( \Delta P \) and GPF.

An estimate of the individual contributions of these changes in \( \Delta P \) and GPF to the observed increase in SNGFR may be obtained from calculation of the effects of isolated changes in \( \Delta P \) and GPF, general results for which are reported elsewhere (14). Of the observed increase in SNGFR following uninephrectomy (~20 nl/min), approximately 5 nl/min appears to be due to the increase in \( \Delta P \), while roughly 15 nl/min is attributable to the rise in GPF. Thus, as has been the case most often in our studies of the dynamics of glomerular ultrafiltration (10, 12, 15, 24), changes in GPF have the most pronounced influence on SNGFR in the rat.

The finding that \( K_f \) does not differ between nephrectomized and nonnephrectomized animals implies a) that \( k \) and \( S \) must both have remained unchanged by uninephrectomy, or b) that \( k \) and \( S \) changed inversely, such that the product of \( k \) and \( S \) remained unchanged after uninephrectomy. It is not possible from the present data to distinguish between these possibilities. Reports in the literature concerning changes in glomerular size following reduction in total renal mass are conflicting (2, 3, 25, 27). The most rigorous study to date, that of Vančura et al. (27), involved isolation of glomeruli by differential sieving and centrifugation. These workers found no significant differences in glomerular diameters of mice before and up to 20 days after uninephrectomy. Whereas quantitative data on glomerular size were not obtained in the present study, no obvious differences in glomerular diameters in vivo were apparent between control and experimental rats. The finding in this study that the \( K_f \) value in uninephrectomized rats is the same as the value reported previously for nonnephrectomized rats, together with this evidence that surface area might not increase, suggests that \( k \), the effective hydraulic permeability of the glomerular capillary wall, is not affected by uninephrectomy. The possibility remains, however, that estimates of glomerular diameter are not a reliable guide to the true glomerular capillary surface area. If this is the case, and increases in \( S \) result from uninephrectomy, the present finding that \( K_f \) following uninephrectomy is the same as in nonnephrectomized animals requires that \( k \) must have declined.

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