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Terrance M. Daugharty, … , Paul F. Mercer, Barry M. Brenner

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Research Article

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Dynamics of Glomerular Ultrafiltration in the Rat

V. RESPONSE TO ISCHEMIC INJURY

TERRANCE M. DAUGHARTY, IRIS F. UEKI, PAUL F. MERCER, and BARRY M. BRENNER

From the Departments of Medicine, Veterans Administration Hospital, San Francisco, California and the University of California, San Francisco, California 94121

ABSTRACT An experimental model of postischemic, acute renal failure has been developed in Wistar rats with surface glomeruli, thereby making possible a direct assessment of the mechanisms responsible for the fall in glomerular filtration rate that characterizes this disorder. Whole kidney and cortical single nephron filtration rates were reduced proportionately, on average by approximately 40%, after 3 h of nearly complete occlusion of the ipsilateral renal artery. The possibility of a significant transtubular leak of inulin was excluded. This decline in filtration rate occurred in the absence of measured changes in mean arterial pressure, mean glomerular transcapillary hydrostatic pressure, or net ultrafiltration pressure at afferent and efferent ends of the glomerular capillary. Net ultrafiltration pressure at the efferent end of the capillary approached zero both before and after ischemic injury, demonstrating that filtration pressure equilibrium was achieved throughout this study. Single nephron filtration fraction remained unchanged, indicating that the fall in filtration rate was accompanied by a proportional decline in glomerular plasma flow. The results indicate that the fall in filtration rate was solely the consequence of this fall in glomerular plasma flow. Since filtration rate per nephron is equal to the product of the ultrafiltration coefficient and mean ultrafiltration pressure, this product must also have fallen in proportion to the decline in glomerular plasma flow. Evidence is presented to indicate that a change in ultrafiltration coefficient is not required to account for the observed fall in filtration rate. The reduction in glomerular plasma flow, occurring in the absence of a concomitant decline in mean glomerular capillary hydrostatic pressure, resulted from large and proportional increases in afferent and efferent arteriolar resistances. These resistance changes appear to play a fundamental role in the pathogenesis of this form of acute renal failure.

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Dr. Brenner is a Medical Investigator and Dr. Daugharty a Clinical Investigator of the Veterans Administration. Dr. Mercer was on sabbatical leave from the Department of Physiology, the University of Western Ontario, London, Canada.

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INTRODUCTION

Despite the frequency with which acute renal failure is encountered in clinical medicine and the relative ease with which this disorder can be reproduced experimentally, the mechanism(s) responsible for the reduction in glomerular filtration rate, one of the hallmark features of this disorder, has yet to be clearly delineated. This is not entirely surprising in that, until recently, a quantitative formulation of the pressures and flows governing ultrafiltration has been lacking, owing to the extreme infrequency with which glomeruli are encountered as accessible surface structures in the mammal. This limitation to the direct study of the dynamics of glomerular transcapillary fluid exchange has been overcome in the past few years, however, largely as a consequence of the discovery of a mutant strain of Wistar rats (the so-called Munich-Wistar strain [1]) possessing surface glomeruli. Recent studies from this laboratory, employing this unique strain of rats, together with highly sensitive servo-null micropressure transducers and ultramicroprotein assay methods, have provided a considerable body of data (1–4) which not only serves to characterize glomerular dynamics in the physiologically normal rat, but which can also provide a much needed frame of reference against which to compare a number of clinically relevant, experimentally induced disorders of glomerular function.

The present study was undertaken in an effort to gain insight into one such disorder, namely, an experimental model of acute, postischemic renal failure, and to apply appropriate techniques to characterize the glomerular transcapillary forces responsible for the accompanying decline in glomerular filtration rate.

GLOSSARY OF SYMBOLS

$\overline{AP}$	Mean femoral arterial pressure, mm Hg.
C	Protein concentration, g/100 ml.
EABF	Efferent arteriolar blood flow, nl/min.
GBF, GPF	Glomerular blood flow and plasma flow, respectively, nl/min.
Hct_A	Blood hematocrit in femoral artery or afferent arteriole.
k	Effective hydraulic permeability, nl/(s·mm Hg·cm²).
K_f	Ultrafiltration coefficient, nl/(s·mm Hg) or nl/(min·mm Hg).
P	Hydrostatic pressure, mm Hg.
P_{UF}	Net ultrafiltration pressure, mm Hg.
ΔP	Transmembrane hydrostatic pressure difference, $P_{GC} - P_T$, mm Hg.
π	Colloid osmotic pressure, mm Hg.
$\Delta\pi$	Transmembrane osmotic pressure difference, $\pi_{GC} - \pi_T$, mm Hg.
R	Resistance to blood flow, dyn·s·cm^{-5}.
R_{TA}	Total arteriolar resistance, $R_A + R_E$, 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.

SUPERSCRIPT

—	Mean value.

SUBSCRIPTS

A	Afferent arteriole.
C	Peritubular capillary.
E	Efferent arteriole.
GC	Glomerular capillary.
T	Proximal tubule.

METHODS

Experiments were performed in Munich-Wistar rats ranging in weight from 161–320 g. Each rat was allowed free access to water and a standard rat pellet diet until the morning of study. After anesthetization with Inactin intraperitoneally (100 mg/kg body weight) the rat was placed on a temperature-regulated micropuncture table and prepared for clearance and/or micropuncture study in the manner previously described for this laboratory (1–6). In addition to this routine preparation, a loose snare of surgical silk was inserted so as to encircle the left renal artery for subsequent use in reducing blood flow to the left kidney. About 15 min before completion of surgery, a continuous intravenous infusion of 10% inulin in isotonic saline was begun at the rate of 0.02 ml/min. This resulted in plasma inulin concentrations of approximately 1 mg/ml.

Effect of 3 h of partial left renal arterial occlusion on GFR and urine composition. The effects of 3 h of severe ischemia on whole kidney (GFR) and cortical single nephron (SNGFR) glomerular filtration rates were examined in seven rats. Beginning 45 min after completion of surgery, three to five collections of urine were obtained from each kidney for determination of volume flow rate and inulin concentration. Simultaneously, two to four exactly timed (1–2 min) total collections of proximal tubule fluid were obtained from surface nephrons in the left kidney for determination of volume flow rate and inulin concentration. In four of these rats, tubule fluid collections were obtained from randomly selected segments of surface proximal tubules; in the remaining three and in two additional rats not otherwise studied, collections of tubule fluid were obtained from either first or last accessible segments of surface proximal tubules. These first and last segments, examined to determine whether inulin leaks out of proximal tubules as a result of ischemic injury, were identified by observing the passage of lissamine green which was injected rapidly (0.04 ml of a 5% solution) into the left jugular vein. Tubule fluid was collected with sharpened micropipettes (8–12 μm OD), using the technique of controlled suction previously validated for this laboratory (7). In addition, two to three samples of femoral arterial blood were obtained for determination of hematocrit and plasma inulin concentration. Femoral arterial blood pressure ($\overline{AP}$) was monitored using a pressure transducer (model P23AA, Statham Instruments, Inc., Oxnard, Calif.) attached to an electronic recorder (model 7712, Hewlett-Packard Co., Palo Alto, Calif.).

Following these control observations, the left renal arterial snare was tightened progressively until arterial pulsations distal to the snare were abolished and the gross appearance of the kidney became shrunken, pale, and slightly cyanotic. These changes were accompanied by uniform collapse of all surface tubule segments and by cessation of urine flow. In all instances, the degree of occlusion of the left renal artery was carefully monitored to insure that blood flow was not completely abolished, but only drastically reduced. As an end point, blood flow in surface peritubular capillaries was reduced to a degree sufficient to slow markedly, but not abolish, the movement of erythrocytes through the capillaries. That glomerular filtration had indeed ceased was verified by the intravenous injection of lissamine green. Dye uniformly failed to appear in surface nephrons during the ischemic period. Occlusion was maintained for exactly 3 h in each rat. During occlusion the microscopic appearance of the surface of the kidney was monitored repeatedly and the above described alterations in appearance and function were maintained unchanged.

At the end of this 3 h period of ischemia the occluding snare was removed. Vigorous renal arterial pulsations returned almost immediately and, within the subsequent 10–15 min, kidney size and surface capillary blood flow appeared to return toward normal. In this same period of time, surface nephrons were noted to fill with fluid and urine formation was noted to resume. Since the infusion of inulin was withheld during the period of occlusion, priming and sustaining infusions of 10% inulin in isotonic saline were readministered at rates which yielded final plasma inulin concentrations of approximately 1 mg/ml. These repeat infusions of inulin were begun within 5 min of release of renal arterial constriction. After 20 min of equilibration, measurements of GFR were repeated for left (clamped) and right (unclamped) kidneys in each rat, the latter values serving as the time control for the former. Concurrently, samples of proximal tubule fluid were recollected from sites previously punctured, for repeat determination of

SNGFR. To obtain a similar time control for SNGFR determinations, we elected not to study the right (unclamped) kidney in comparison to the left, but rather to repeat the protocol in other rats exactly as described above with the exception that the left renal artery was not clamped. A separate group of four rats was employed for this purpose, with two to four late proximal tubules being studied in each rat before and after sham occlusion of the left renal artery. Again the recollection micropuncture technique was employed.

A second method for evaluating the validity of the use of inulin as an ideal marker of glomerular ultrafiltration in the postischemic kidney was based on the recovery in urine of [^{3}H]inulin microinjected into surface proximal tubules, according to the method of Gottschalk, Morel, and Mylle (8). In each of three rats, both ureters were catheterized with PE 50 tubing. To permit rapid serial urine collections, rats were made diuretic by intravenous infusion of furosemide (1 mg/kg prime and/h). Approximately 5 nl of [^{3}H]inulin (New England Nuclear Corp., Boston, Mass.) in nigrosin-stained isotonic saline was used for microinjection into early and midproximal segments, identified with the aid of lissamine green. Injections were made at rates slow enough to prevent retrograde flow. Ureteral urine was collected into 1-ml cylinders graduated in units of 0.01 ml. Urine collections were started at the beginning of each microinjection. Three consecutive 10-min collections were made from each catheter. To each sample of collected urine was added sufficient cold urine to bring the volume to 1.0 ml. Cold urine was obtained before isotope injections. Calibration droplets equal in volume to the volumes microinjected were deposited into 1.0 ml of cold urine to serve as reference standards. Reference standards and experimental urine samples were each washed with 7 ml of Aquasol (New England Nuclear Corp.) into vials containing 2 ml of distilled water and mixed thoroughly. This liquid scintillation counting mixture formed a gel which prevented settling of isotope. Radioactivity was measured in a liquid scintillation counter (model 3380, Packard Tri-Carb, Packard Instrument Co., Inc., Downers Grove, Ill.). Samples were counted for 50 min or for a total of 10,000 counts above background. Reference standards always reached 10,000 counts above background.

Glomerular dynamics before and after ischemic injury. In 10 additional rats the effects of 3 h of left renal ischemia on the glomerular transcapillary determinants of ultrafiltration were studied. In these rats, beginning about 45 min after completion of surgery, exactly timed (1–2 min) total collections of fluid were obtained from late segments of two to four surface proximal tubules for determination of volume flow rate and inulin concentration. Simultaneously, two to three samples of femoral arterial blood were obtained for measurement of hematocrit and plasma inulin and protein concentrations. The concentrations of these substances are taken as equal to their concentrations in afferent arteriolar plasma. In addition, samples of blood from two to three surface efferent arterioles were obtained for determination of postglomerular plasma protein concentration. $\overline{AP}$ was monitored throughout. Hydrostatic pressures within single capillaries of surface glomeruli ($\bar{P}_{GC}$),[1] peritubule capillaries (P_C), and proximal tubules (P_T) were measured using continuous recording, electronic servo-null micropressure transducer techniques (9–11). For these measurements, 0.5 M NaCl-containing micropipettes with outer tip diameters of 2–3 μm were used, and capillary entry was accomplished under stereomicroscopic control. Hydraulic output from the servo system was coupled electronically to a second channel of the Hewlett-Packard recorder by means of a pressure transducer (model P23Db, Statham Instruments, Inc.). Accuracy, frequency response, and stability features of this servo system have been described in detail previously (11).

After completion of these measurements, the left renal artery was nearly completely occluded for 3 h, in the manner already described. Thereafter, the occlusion was relieved and each of the above measurements repeated. Repeat collections of proximal tubule fluid were obtained using recollection techniques. Repeat collections of efferent arteriolar blood and measurements of P_C and P_T were obtained from sites not previously punctured. In many rats, since only one glomerulus was present on the kidney surface, repeat measurements of $\bar{P}_{GC}$ necessitated entry into capillaries of a previously punctured glomerulus.

Analytical techniques. The volume of fluid collected from individual proximal tubules was determined 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 (12). Inulin concentration in plasma was determined by the macroanthrone method of Führ, Kaczmarczyk, and Krüttgen (13). Protein concentration in efferent arteriolar (C_E) and femoral arterial (C_A) blood plasma was determined, usually in duplicate, with an ultramicrocolorimeter[2] using a recently described microadaptation (14) of the method of Lowry, Rosebrough, Farr, and Randall (15).

Calculations. SNGFR:

$$\text{SNGFR} = (\text{TF/P})_{IN} \cdot V_{TF} \tag{1}$$

where $(\text{TF/P})_{IN}$ and V_{TF} refer to the tubule fluid to plasma inulin concentration ratio and tubule fluid flow rate, respectively.

Single nephron filtration fraction (SNFF):

$$\text{SNFF} = 1 - \frac{C_A}{C_E} \tag{2}$$

where C_A and C_E denote afferent and efferent arteriolar plasma protein concentrations, respectively.

Volume flow rate of plasma entering the glomerulus, glomerular plasma flow (GPF):

$$\text{GPF} = \frac{\text{SNGFR}}{\text{SNFF}} \tag{3}$$

Glomerular blood flow (GBF):

$$\text{GBF} = \frac{\text{GPF}}{1 - \text{Hct}_A} \tag{4}$$

where Hct_A, the hematocrit of afferent arteriolar blood, is taken as being equal to femoral arterial hematocrit.

[1] The values for P_{GC} reported in the present study represent time averages. The term $\bar{P}_{GC}$ represents P_{GC} averaged over the length of the glomerular capillary, the justification for which has been discussed previously (2).

[2] Designed and constructed by Dr. Gerald Vurek, Laboratory of Technical Development, National Heart and Lung Institute, Bethesda, Md.

Efferent arteriolar blood flow:

$$\text{EABF} = \text{GBF} - \text{SNGFR} \quad (5)$$

Resistance per single afferent arteriole:

$$R_A = \frac{\overline{AP} - \overline{P}_{GC}}{\text{GBF}} \times (7.962 \times 10^{10}) \quad (6)$$

where the factor 7.962×10^{10} is used to give resistance in units of dyn·s·cm^{-5} when $\overline{AP}$ and $\overline{P}_{GC}$ are expressed in mm Hg and GBF in nl/min.

Resistance per single efferent arteriole:

$$R_E = \frac{\overline{P}_{GC} - P_C}{\text{EABF}} \times (7.962 \times 10^{10}) \quad (7)$$

Total arteriolar resistance for a single pre- to postglomerular vascular unit:

$$R_{TA} = R_A + R_E \quad (8)$$

Estimates of the net ultrafiltration pressure (P_{UF}) at the afferent- and efferent-most portions of the glomerular capillary:[3]

$$P_{UF_A} = \overline{P}_{GC} - P_T - \pi_A \quad (9)$$

$$P_{UF_E} = \overline{P}_{GC} - P_T - \pi_E \quad (10)$$

where π_A and π_E, afferent and efferent arteriolar colloid osmotic pressures, were calculated from femoral arterial and efferent arteriolar plasma protein concentrations using the Landis-Pappenheimer equation (16). Equations 9 and 10 contain the assumption that the colloid osmotic pressure of fluid in Bowman's space (π_T) is negligible. This assumption has been validated by the finding that the protein concentration of fluid in Bowman's space, both before and after 3 h of renal ischemia, is less than 200 mg/100 ml. Accordingly, π_T is well below 1 mm Hg.

Mean net glomerular transcapillary hydrostatic pressure:

$$\overline{\Delta P} = P_{GC} - P_T \quad (11)$$

The percent recovery of injected [^{3}H]inulin:

$$\text{Percent recovery} = \frac{[^3\text{H}]\text{inulin in urine}}{[^3\text{H}]\text{inulin in injectate}} \times 100 \quad (12)$$

RESULTS

Evaluation of inulin as a valid marker of GFR after renal ischemia. Justification for the use of inulin as an ideal marker of GFR after ischemic injury was obtained from two sets of evidence. First we compared absolute values of SNGFR in first and last segments of surface proximal tubules as well as percentage changes in recollection values of SNGFR at these sites. Before ischemia, values for SNGFR averaged 36.5±3.7 SE nl/min ($n = 5$) and 34.6±3.9 (5) at first and last accessible segments, respectively ($P > 0.5$). After ischemia, values at these respective sites averaged 17.1±4.1 nl/min and 15.6±4.7. These reductions in SNGFR were uniform and highly significant ($P < 0.001$), averaging 56±8 and 58±10%, respectively, but were not significantly different from one another ($P > 0.5$). A comparison of paired changes in SNGFR (postocclusion vs. preocclusion) at first vs. last sites in each rat is shown in Fig. 1. It can be seen that comparable reductions obtained at first and last collection sites irrespective of the magnitude of the decline in SNGFR. The ratio ΔSNGFR first segment/ΔSNGFR last segment averaged 0.97±0.04, a value not significantly different from unity ($P > 0.4$). Moreover, changes in SNGFR after ischemia were essentially identical to changes in whole kidney GFR, averaging 49±5 (7) and 52±8% (7), respectively ($P > 0.5$).

The second set of evidence justifying the use of inulin as a valid glomerular marker was obtained from proximal tubule microinjection studies. Six microinjections of [^{3}H]inulin were performed in three rats after ischemic injury. Ipsilateral recoveries of [^{3}H]-inulin were essentially complete after microinjection, averaging 101±1% (range: 98–106%). Recovery from the contralateral kidney was never in excess of background. This evidence demonstrating impermeability of the tubule epithelium to inulin after ischemic injury was obtained in experimental kidneys in which whole kidney inulin clearances were reduced by 24, 36, and 39% for the three rats studied. Since microinjected [^{3}H]inulin was essentially completely recovered, these reductions in whole kidney clearances of inulin could only have occurred as a result of true reductions in GFR.

Effects of 3 h of unilateral renal ischemia on GFR and urine composition. Table I summarizes average values for $\overline{AP}$, systemic hematocrit, as well as GFR, urine flow, urine/plasma inulin concentration ratios,

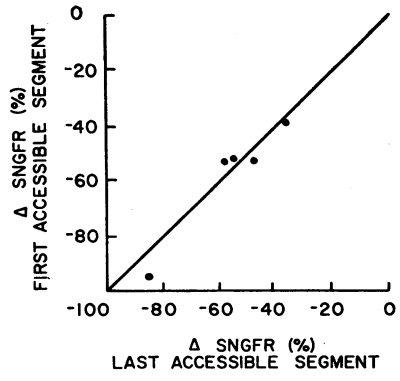

FIGURE 1 Comparison of percentage changes in SNGFR measured at first and last accessible proximal tubule segment collection sites before and after ischemic injury in individual rats.

[3] The use of this equation assumes the axial variation in P_{GC} to be negligible. The justification for this assumption is discussed in detail elsewhere (2).

TABLE I

Effect of 3 h of Left Renal Ischemia on Bilateral Renal Function

			Left kidney					Right kidney			
	$\overline{AP}$	Hct	SNGFR	GFR	Urine flow	$\left(\frac{U}{\bar{P}}\right)_{IN}$	$U_{[Na]}$	GFR	Urine flow	$\left(\frac{U}{\bar{P}}\right)_{IN}$	$U_{[Na]}$
	mm Hg	%	*nl/min*	*ml/min*	*μl/min*		*meq/liter*	*ml/min*	*μl/min*		*meq/liter*
Preleft renal ischemia											
Mean	106	52	33	0.84	3.7	213	56.4	0.91	4.2	230	66.2
±SE	3	1	3	0.07	0.8	16	12.5	0.03	0.2	9	13.1
N rats	7	7	7	7	7	7	5	5	5	5	5
Postleft renal ischemia											
Mean	102	52	17	0.41	4.4	99	132.8	0.99	5.3	189	151.2
±SE	2	1	3	0.08	0.9	10	28.0	0.08	0.2	9	32.4
N rats	7	7	7	7	7	7	5	5	5	5	5
Mean Δ, %	−3.2	+0.2	−48.6	−51.7	+10.8	−52.6	+141	+10.5	+28.7	−16.8	+126
±SE	3.1	1.4	5.1	8.4	20.7	4.9	43	11.6	6.6	5.8	14
P Value	>0.2	>0.5	<0.001	<0.001	>0.5	<0.001	<0.05	>0.5	<0.001	<0.05	<0.001

and urinary sodium concentrations for left (experimental) and right (control) kidneys both before and after left renal ischemia. Mean values of SNGFR for the experimental kidney are also given. $\overline{AP}$ and Hct remained essentially unchanged. For these seven rats, ischemia resulted in uniform declines in SNGFR averaging 49%, which, as already noted, paralleled declines in whole kidney GFR. That these declines in filtration rate were the specific consequence of temporary renal ischemia is given by the findings (*a*) that values for GFR for the nonclamped right kidney failed to exhibit similar declines, changing on average by + 10.5±11.6% ($P > 0.5$), and (*b*) values for SNGFR in four rats subjected to sham clamping of the left renal artery changed (relative to presham-clamped control values) by an average of − 3.6±7.6% ($n = 16$ nephrons) ($P > 0.5$).

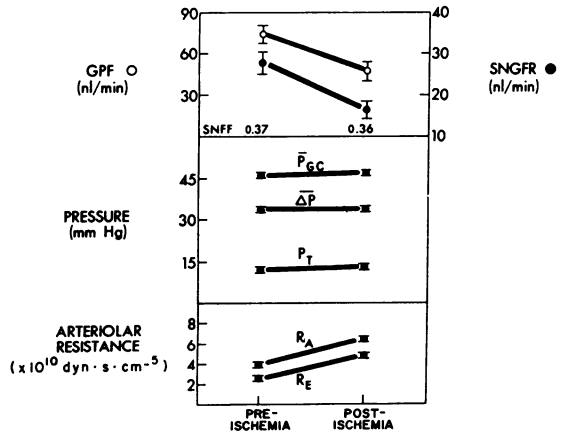

FIGURE 2 Summary of effects of ipsilateral ischemic injury on several measures of surface nephron and microvascular function.

As shown in Table I, temporary ischemia of the left kidney was associated with a large decline in ipsilateral fractional water reabsorption (U/P inulin concentration declined an average of 53%). As a result, despite the large fall in filtration rate, urine flow remained relatively unchanged. While a statistically significant decline in the mean U/P inulin concentration ratio was measured on the nonclamped side, the magnitude of this decline tended to be small. For individual rats, U/P inulin ratios for the right kidney ranged from 177–285 before to 144–253 after contralateral ischemia, compared with values for corresponding periods from the left kidney ranging from 138–266 before to 56–135 after arterial occlusion. Although urinary sodium concentration increased on the ipsilateral side in a manner typical of that observed in clinical forms of acute renal failure, this finding can only be regarded as being compatible with, but not convincing evidence for, a selective defect in transtubular transport of sodium. This is so because of the finding of a comparable average increase in urinary sodium concentration on the nonclamped side, a well-documented and predictable response to acute contralateral renal arterial constriction (17–20).

Additional evidence in support of ipsilateral injury of renal tubule function derives, however, from the findings that after release of occlusion, urine from the experimental kidney was colorless and when examined microscopically (in three rats) was found to contain large numbers of erythrocytes, renal tubule epithelial cells, and epithelial cell and granular casts. In contrast, urine from the contralateral control kidney, obtained simultaneously, regularly appeared dark yellow in color and contained neither cells nor formed elements.

TABLE II

Effect of 3 h of Ipsilateral Renal Ischemia on the Measured

Rat no.	Preocclusion												
	$\overline{AP}$	SNGFR	C_A	C_E	SNFF	GPF	$\overline{P}_{GC}$	P_T	π_A	π_E	P_{UF_A}	P_{UF_E}	$\frac{\pi_E}{\overline{P}_{GC} - P_T}$
	mm Hg	*nl/min*	*g/100 ml*			*nl/min*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	
14		25.6											
		27.0											
		30.0											
	103	27.5	5.4	9.2	0.41	66.6	46	11	17	40	18	−5	1.14
15		35.6											
		34.6											
		45.4											
		36.8											
	115	38.1	5.9	8.9	0.34	113.1	46	10	20	38	16	−2	1.06
16		29.4											
		19.5											
		23.5											
		17.4											
	123	22.5	5.2	8.7	0.40	55.9	46	11	16	36	19	−1	1.03
17		13.7											
		14.1											
		10.5											
	118	12.8	5.9	8.7	0.32	39.7	44	14	20	36	10	−6	1.20
18		20.9											
		21.6											
		17.7											
	128	20.1	5.7	8.1	0.30	67.8	52	12	19	32	21	8	0.80
19		35.1											
		30.5											
		31.4											
		33.5											
	105	32.6	5.5	8.9	0.38	85.4	45	14	18	38	13	−7	1.22
20		31.2											
		50.4											
		30.5											
		30.1											
	92	35.5	5.2	8.8	0.41	86.9	46	13	16	37	17	−4	1.12
21		28.5											
		37.3											
	102	32.9	5.4	8.5	0.36	90.2	47	11	17	35	19	1	0.97
22		28.4											
		26.0											
		39.3											
	112	31.2	5.4	9.0	0.40	78.1	44	13	17	38	14	−7	1.22
23		19.6											
		25.7											
		24.9											
		18.7											
	100	22.2	4.9	8.4	0.42	53.3	44	11	15	34	18	−1	1.03
Mean	110	27.5	5.5	8.8	0.37	73.7	46	12	18	36	16	−2	1.08
±SE	4	2.5	0.1	0.1	0.04	6.8	1	0.4	0.5	0.7	1	1	0.04
Mean Δ from initial													
±SE													
P value													

Postocclusion

$\overline{AP}$	SNGFR	C_A	C_E	SNFF	GPF	$\overline{P}_{GC}$	P_T	π_A	π_E	P_{UF_A}	P_{UF_E}	$\frac{\pi_E}{\overline{P}_{GC} - P_T}$
mm Hg	*nl/min*	*g/100 ml*			*nl/min*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	
	13.5											
	13.5											
	18.9											
96	15.3	4.9	7.4	0.34	45.2	44	11	15	28	18	5	0.85
	27.7											
	22.5											
	34.3											
	36.7											
123	30.3	5.8	8.5	0.32	95.3	46	14	19	35	13	−3	1.09
	17.0											
	11.5											
	6.7											
	10.3											
142	11.4	5.6	8.7	0.36	32.0	49	13	18	36	18	0	1.00
	7.5											
	6.7											
	5.5											
107	6.6	5.3	8.1	0.35	18.9	49	13	17	32	19	4	0.89
	15.3											
	13.2											
	11.0											
123	13.2	4.8	7.6	0.37	35.8	52	12	15	29	25	11	0.72
	19.1											
	18.4											
	24.8											
	19.0											
116	20.3	5.5	8.5	0.35	57.8	55	14	18	35	23	6	0.85
	15.3											
	13.8											
	19.2											
	12.9											
93	15.3	5.1	7.7	0.34	45.3	37	13	16	30	8	−6	1.25
	15.2											
	24.6											
100	19.9	5.6	8.5	0.34	58.3	47	14	18	35	15	−2	1.06
	19.7											
	19.5											
	21.8											
101	20.4	5.4	8.5	0.37	55.8	47	12	17	35	18	0	1.00
	7.6											
	9.4											
	15.6											
	11.2											
100	11.0	4.8	8.4	0.43	25.6	44	15	15	34	14	−5	1.17
110	16.4	5.3	8.2	0.36	47.0	47	13	17	33	17	1	0.99
5	2.1	0.1	0.1	0.01	6.9	2	0.4	0.5	0.9	2	2	0.05
+0.3	−41.3%	−0.2	−0.5	−0.019	−38.7%	+1	+1	−1	−3	+0.4	+3	−0.09
3.1	3.1	0.1	0.2	0.014	3.7	1.6	0.6	0.6	1.2	2.0	2	0.06
>0.5	<0.001	>0.2	<0.025	>0.2	<0.001	>0.5	>0.5	>0.2	<0.025	>0.5	>0.1	>0.10

Glomerular dynamics before ischemic injury. Table II and Fig. 2 summarize average values for several measures of nephron and microvascular function obtained before renal artery constriction in 10 normal hydropenic rats. SNGFR averaged 28 nl/min. SNFF averaged 0.37, with individual values ranging from 0.30 to 0.42. Therefore, GPF, calculated using equation 3, averaged 74 nl/min. $\bar{P}_{GC}$ averaged 46 mm Hg, with individual values ranging from 44 to 52 mm Hg. Pressures measured at random sites in surface proximal convolutions averaged 12 mm Hg. Values for P_C averaged 9.6±0.5 mm Hg. The hydrostatic pressure drop along surface afferent arterioles ($\bar{A}\bar{P} - \bar{P}_{GC}$) averaged 64±3 mm Hg, compared with a uniformly smaller pressure drop averaging 36±1 mm Hg ($P < 0.001$) along surface efferent arterioles ($\bar{P}_{GC} - P_C$). Mean values for R_A and R_E are summarized in Fig. 2. On average, afferent arterioles were found to contribute 55% of the total resistance to blood flow (R_{TA}, equation 8) to the level of the smallest accessible peritubular capillaries.

Microassay measurements of total protein concentration in preglomerular (C_A) and efferent arteriolar (C_E) plasma in 10 rats yielded values averaging 5.5 ±0.1 and 8.8±0.1 g/100 ml, respectively. π_A and π_E calculated from these protein concentrations are shown in Table II. As given in equations 9 and 10, it is possible, from measurements of $\Delta\bar{P}$, that is $\bar{P}_{GC} - P_T$, together with these estimates of π_A and π_E, to determine the magnitude of the transmembrane pressure difference favoring ultrafiltration (P_{UF}) across afferent- and efferentmost portions of the glomerular capillary in each rat. As summarized in Table II, $\bar{P}_{GC}$ exceeded the sum of the opposing pressures ($P_T + \pi_A$) at the afferent ends of glomerular capillaries by an average of 16±1 mm Hg. By the efferent ends this imbalance of pressures largely disappeared (Table II). For 10 rats the ratio $\pi_E/(\bar{P}_{GC} - P_T)$ averaged 1.08±0.04, a value not significantly different from unity ($P > 0.05$), indicating that filtration pressure equilibrium obtained under these conditions.

Glomerular dynamics after ischemic injury. Without changing $\bar{A}\bar{P}$, ischemic injury resulted in uniform and highly significant ($P < 0.001$) declines in SNGFR averaging 41% (Table II and Fig. 2). SNFF remained essentially constant; hence GPF fell in proportion to SNGFR. Despite the fall in SNGFR, note that neither $\bar{P}_{GC}$ nor P_T changed significantly; hence ΔP and the pressure drop along the afferent arteriole ($\bar{A}\bar{P} - \bar{P}_{GC}$) remained unchanged. Ischemic injury likewise failed to produce substantial changes in P_C, values averaging 9.1±0.9 mm Hg. Accordingly, the pressure drop along the efferent arteriole ($\bar{P}_{GC} - P_C$) also remained unchanged from preischemic values.

Rates of blood flow through single afferent (GBF) and efferent (EABF) arterioles on the renal cortical surface uniformly declined from average values of 147±13 and 120±11 nl/min before ischemia to 95±13 and 79±11 nl/min after injury, respectively. It follows from equations 6 and 7 that since these declines in arteriolar blood flow occurred without concomitant declines in the axial pressure drops along these arterioles, R_A and R_E were increased by ischemic injury (Fig. 2). These increases averaged 64.5±11.7% ($P < 0.001$) and 74.2±18.4% ($P < 0.005$), respectively. Since these increases in R_A and R_E were of similar magnitudes, the contribution of R_A to the total arteriolar resistance, R_{TA}, remained essentially unchanged, averaging 57.4±1.1%.

After ischemic injury, C_A remained unchanged (Table II) whereas C_E tended to decline slightly, on average to 8.2±0.1 g/100 ml ($P < 0.025$). Values for π_A and π_E are given in Table II. Accordingly, the large and uniform declines in SNGFR occurred despite no significant mean declines in net ultrafiltration pressure at afferent (P_{UF_A}) or efferent (P_{UF_E}) ends of the glomerular capillary (Table II). The ratio $\pi_E/(\bar{P}_{GC} - P_T)$ averaged 0.99±0.05, a value not different from unity ($P > 0.05$), indicating persistence of filtration pressure equilibrium. For paired data, the change in this ratio was likewise not significant statistically ($P > 0.1$).

DISCUSSION

In the Munich-Wistar rats examined for this study, 3 h of unilateral renal ischemia resulted in moderately severe reductions in ipsilateral GFR. Impairment in ipsilateral renal function was found to mimic the clinical disorder of postischemic acute renal failure in other respects, including most notably, the elaboration of a colorless urine rich in sodium, red blood, and renal tubule epithelial cells and epithelial cell casts. In addition, the capacity to reabsorb the same large fraction of the glomerular filtrate as the unclamped kidney was found to be markedly reduced. The declines in the measured values of GFR, shown not to be the consequence of any significant transtubular leak of inulin, involved cortical and juxtamedullary nephrons uniformly, in that the magnitude of reductions in whole kidney GFR and cortical SNGFR were similar in individual rats.

Glomerular ultrafiltration is governed by the imbalance of transcapillary hydrostatic and colloid osmotic pressure differences. At any point along a glomerular capillary the net driving force (P_{UF}) is given by:

$$P_{UF} = \Delta P - \Delta\pi = (P_{GC} - P_T) - (\pi_{GC} - \pi_T) \quad (13)$$

where P_{GC} and P_T are the hydrostatic pressures in the

glomerular capillary and proximal tubule, respectively, and π_{GO} and π_T are the corresponding colloid osmotic pressures. Since tubule fluid is essentially protein-free, π_T is negligible and $\Delta\pi = \pi_{GC}$.

The rate of glomerular ultrafiltration per nephron (SNGFR) may be expressed as

$$\text{SNGFR} = K_f \cdot \bar{P}_{UF} = k \cdot S \cdot \bar{P}_{UF} = k \cdot S \cdot (\overline{\Delta P} - \bar{\pi}_{GC}) \quad (14)$$

where $\bar{P}_{UF}$ is the mean driving pressure (P_{UF} averaged along the length of the capillary), equal to the difference between the mean transcapillary hydrostatic and oncotic pressure differences, $\overline{\Delta P} - \bar{\pi}_{GO}$. K_f, the ultrafiltration coefficient, is the product of the effective hydraulic permeability (k) and surface area (S) of the glomerular capillaries. Since in the present study $\bar{P}_{GC}$ and P_T remained essentially unchanged after ischemic injury, so that $\overline{\Delta P}$ remained essentially unchanged, it follows from equation 14 that the decline in SNGFR following ischemia must have resulted from a decline in K_f, $\bar{P}_{UF}$, or both. Provided that $\bar{P}_{UF}$ could be evaluated from these pressure measurements, equation 14 would allow calculation of K_f from measurements of $\bar{P}_{UF}$ and SNGFR. However, under the conditions of filtration pressure equilibrium which prevailed in this study (equality of ΔP and π_{GO} at the efferent end of the glomerular capillary), it is impossible to estimate $\bar{P}_{UF}$, and thus K_f, due to the uncertainty in determining $\bar{\pi}_{GC}$. This uncertainty results from the fact that since the local rate of ultrafiltration is proportional to the local value of P_{UF}, π_{GO} will increase most rapidly at the afferent end of the capillary. As discussed in detail elsewhere (21), filtration pressure equilibrium requires that the profile of π_{GO} along a capillary be highly nonlinear, and allows for any number of nonlinear profiles to correspond to given measurements of π_A and π_E (21). Curves A and B in Fig. 3 show two possible profiles. For a given initial GPF, curve A corresponds to a larger value of K_f than does curve B. In general, an increase in K_f above the minimum value required to yield equilibrium results in a more rapid approach to equilibrium (as in curve A) but essentially the same final value of π_{GO}, measured as π_E. Since $\bar{P}_{UF}$ is equal to the area between the ΔP and π_{GO} curves as plotted in Fig. 3, $\bar{P}_{UF}$ and therefore K_f cannot be uniquely determined from the available measurements under conditions of filtration pressure equilibrium.

The present study provides an excellent example of this uncertainty in determining $\bar{P}_{UF}$ and K_f under equilibrium conditions. As summarized in Fig. 2, SNGFR was markedly reduced by ischemic injury, whereas SNFF remained relatively unchanged. Accordingly, SNGFR must have declined in proportion to GPF, indicating, as previously reported (2–4, 21),

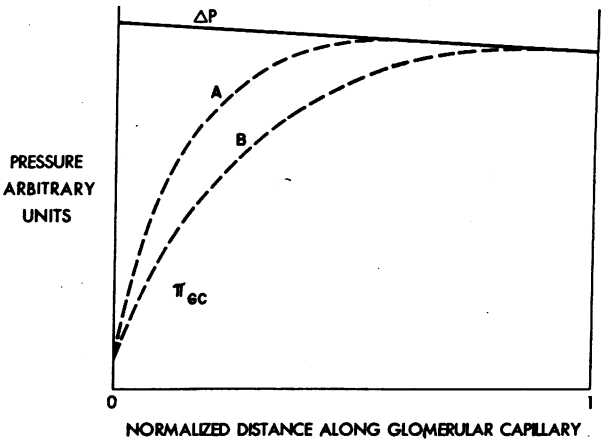

FIGURE 3 Hydrostatic and colloid osmotic pressure profiles along an idealized glomerular capillary. $\Delta P = P_{GO} - P_T$. Since $\Delta\pi = \pi_{GO} - \pi_T$ and since $\pi_T \sim 0$, $\Delta\pi = \pi_{GO}$.

that SNGFR is highly plasma-flow dependent. Some insight into the mechanism(s) responsible for this plasma-flow dependence of SNGFR is gained by reviewing the results of measurements of glomerular transcapillary hydrostatic and oncotic pressure obtained in this study. As noted, since values for $\overline{\Delta P}$ and π_A after ischemic injury were essentially unchanged from preischemic values, the net driving pressure at the afferent end of the glomerular capillary (P_{UF_A}) was likewise unchanged. Furthermore, equality of ΔP and π_E obtained both before and after ischemia, indicating that the net driving pressure at the efferent end of the glomerular capillary (P_{UF_E}) remained essentially zero throughout this study.

Although a term for the rate of plasma flow through the glomerulus does not appear explicitly in equation 14, the rate of flow must modify the effective driving force for ultrafiltration. The mechanism whereby a decrease in GPF brings about a proportional decrease in SNGFR might involve flow-induced declines in K_f, $\bar{P}_{UF}$, or both. Fig. 3 helps to illustrate these possibilities. Let curve B represent the actual π_{GO} profile before ischemic injury. If K_f decreases in proportion to GPF, curve B will also represent the π_{GO} profile after ischemic injury. In this case, the area between the ΔP and π_{GO} curves (equal to $\bar{P}_{UF}$) will remain constant, and SNGFR will decrease solely as a result of the flow-induced decline in K_f. Alternatively, if K_f remains unchanged after ischemia, the decrease in GPF will shift the π_{GO} profile to the left, as from curve B to curve A in Fig. 3, and the decline in SNGFR will result solely from the ensuing reduction in $\bar{P}_{UF}$. Note that for both of the possibilities just considered, no changes in initial (π_A) and final (π_E) values of π_{GO} are required. In the present study then, where a marked

TABLE III

Plasma-Flow Dependence of SNGFR. Comparison of Predicted with Observed Values

Condition	SNGFR	
	Predicted	Observed
	nl/min	*nl/min*
Preischemia	24.7±2.2 (10)	27.5±2.5 (10)
Postischemia	15.8±1.9 (10)	16.4±2.1 (10)

Observed SNGFR values are given as means ±SE. Predicted refers to values calculated using the model (21), assuming K_f to equal 0.08 nl/(s·mm Hg) and to be constant for both conditions. An axial pressure drop along the glomerular capillary of 1 mm Hg has been assumed, the justification for which is given elsewhere (2). Numbers in parentheses refer to *n* animals.

decline in SNGFR was accomplished without appreciable changes in π_A, π_E, or ΔP, the persistence of filtration pressure equilibrium makes it impossible to determine the relative contributions of changes in K_f and $\overline{P}_{UF}$ to the total change in SNGFR.

Nevertheless, it is possible to gain considerable insight into the mechanisms responsible for the observed plasma-flow dependence of SNGFR after ischemic injury by use of a recently developed mathematical model (21) which simulates the known dynamics of glomerular ultrafiltration. In this model, conservation of mass and the Starling hypothesis have been used to derive a differential equation giving the rate of change of protein concentration with distance along an idealized glomerular capillary. The numerical solution to this equation, given in detail elsewhere (21), can be used to compute π_{GC} profiles for given values of C_A, K_f, $\overline{\Delta P}$, and GPF. Application of the model to the present study is readily accomplished in that values for all of the necessary inputs except K_f were measured. For reasons already discussed, a value for K_f cannot be determined under conditions of filtration pressure equilibrium. A unique value for K_f of the glomerulus of this mutant rat has, however, recently been obtained by Deen, Troy, Robertson, and Brenner (4) under conditions of very high GPF, which had the desired effect of preventing achievement of filtration pressure equilibrium. Under these disequilibrium conditions only one π_{GC} profile can fit the experimental data, yielding only one value of K_f. Moreover, this unique value of K_f, 0.08 nl/(s·mm Hg), was found to be essentially constant despite almost twofold variations in GPF. Of particular importance to the present study, this same value of K_f was found to be sufficiently large to yield equilibrium at the lower rates of GPF which obtain in normal hydropenic rats (4). As shown in Table III, use of this same K_f value together with measured values of C_A, $\overline{\Delta P}$, and GPF from the 10 normal hydropenic rats studied before ischemic injury in the present study leads to remarkably close agreement between predicted and observed values for SNGFR. Note that similarly close agreement between predicted and observed values obtains for inputs measured after ischemic injury. Since in the latter calculation K_f has been held constant at the preischemic value of 0.08 nl/(s·mm Hg), the present evidence suggests, but by no means establishes, that the decline in SNGFR after ischemic injury was mediated solely by a decline in $\overline{P}_{UF}$ resulting from a plasma-flow induced shift in the π_{GC} curve so that equality with $\overline{\Delta P}$ is achieved at a site nearer the afferent end of the glomerular capillary than was the case before ischemia (analogous to a shift in the π_{GC} profile from curve B to curve A in Fig. 3).

The present findings thus provide a potentially ubiquitous explanation to account, at least in part, for the fall in GFR that regularly occurs in a variety of forms of acute renal failure. In this study, the observed decline in SNGFR could be attributed solely to the decline in $\overline{P}_{UF}$, the latter due to a rise in $\overline{\pi}_{GC}$. The present studies by no means exclude the possibility that $\overline{P}_{UF}$ might also fall due to a decline in $\overline{\Delta P}$ (equation 14). While not observed in the present study, such a decline in $\overline{\Delta P}$ (due either to a fall in $\overline{P}_{GC}$, a rise in P_T, or both) would be expected to result in reductions in filtration rate more severe than those produced in the present study (that is, due to a fall in GPF alone). Likewise, more severe reductions in filtration rate would be expected were a fall in GPF to be accompanied by a concomitant decline in K_f. Obviously, were declines in $\overline{\Delta P}$ or K_f, or both, to be superimposd on a flow-induced decline in $\overline{P}_{UF}$, GFR would then be expected to fall more than in proportion to the fall in GPF (i.e., filtration fraction would fall).

It should be readily evident from the foregoing that glomerular ultrafiltration is determined primarily by a dynamic interplay of pressures and flows within and across the glomerular capillary wall. Until now, an assessment of all of the critical pressures and flows has been lacking in experimental studies of the defect in glomerular ultrafiltration in acute renal failure, largely because of the inaccessibility of the glomerulus to direct examination in the mammal. Nevertheless, an extensive body of literature has accumulated on this topic which, in general, has identified alterations in the glomerular microcirculation as being causally responsible, at least in part, for the observed defects in ultrafiltration (a comprehensive bibliography is given in [22]).

In the present study, reductions in GPF occurred in the absence of concomitant declines in $\overline{P}_{GC}$ and were,

therefore, the result of proportional increases in R_A and R_E. These increases in resistance are presumed to correspond to reductions in the luminal diameters of afferent and efferent arterioles induced by renal ischemia. Of interest, Sheehan and Davis (23) and others more recently (24–28) have called attention to the persistence of impaired organ blood flow (kidney, brain, heart) following relief of temporary, but severe, arterial occlusion (the so-called no-reflow phenomenon). Leaf has suggested (25) and he and co-workers (27, 28) and others (26) have provided evidence to indicate that capillary endothelial cells tend to swell after severe ischemia and that such swelling might account, at least in part, for the persistence of impaired organ perfusion. In support of this possibility, perfusion of ischemic organs with solutions of hypertonic mannitol was found by these workers (27, 28) to improve organ blood flow, presumably by an effect of this hypertonic, relatively impermeant solute to reduce postischemic cell swelling. Whether cell swelling accounts for the reduction in GPF and the increases in R_A and R_E observed after ischemic injury in the present study remains to be determined. Based on preliminary observations using light and electron microscopy, however, we have been unable to demonstrate swelling of endothelial cells in glomerular capillaries of several kidneys which exhibited typical alterations in GPF, SNGFR, R_A, and R_E. Moreover, additional preliminary evidence has been obtained to indicate that these postischemic alterations in GPF, SNGFR, and R_A and R_E can be reversed by expansion of plasma volume with donor rat plasma (2.5% body weight), an effect clearly not attributable to the osmotic action of hypertonic solute. More work will obviously be required before the precise mechanism(s) responsible for the postischemic increase in microvascular resistances observed in the present study can be established. It seems relatively clear, however, that these increases in resistance to blood flow constitute a fundamental defect in this form of acute renal failure.

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