Blood Flow Dependence of Postglomerular Fluid Transfer and Glomerulotubular Balance

VALENTINA KON, MARY L. HUGHES, and IEKUNI ICHIKAWA, *Laboratory of Renal Physiology, The Children's Hospital and Laboratory of Kidney and Electrolyte Physiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115*

ABSTRACT The rate of blood flow entering a capillary network can, in some vascular systems, regulate capillary surface area and the rate of fluid and solute transfer. To determine whether such a mechanism exists in the renal peritubular capillary, we performed micropuncture studies in 28 rats during relatively low and high efferent arteriolar blood flow (EABF). High EABF was achieved by intravenous infusion of isoncotic plasma (group 1: from 120±11 to 301±49 nl/min [±SE]); whole blood with high hematocrit (~75 vol %) (group 2: from 141±14 to 252±31 nl/min); or acetylcholine (group 3: from 193±20 to 266±26 nl/min). In group 1 rats, plasma infusion caused an increase in single nephron glomerular filtration rate (SNGFR), on average, from 23.2±2.4 to 45.2±3.9 nl/min, owing primarily to increased glomerular plasma flow rate (from 63±5 to 210±21 nl/min). The rate of fluid uptake by the peritubular capillary, assessed by the absolute rate of proximal fluid reabsorption (APR), also rose significantly, on average from 10.5±1.2 to 17.5±2.4 nl/min. This rise in APR was associated with near constancy in mean transcapillary hydraulic ($\overline{\Delta P}_C$) and oncotic ($\overline{\Delta\Pi}_C$) pressure differences, and was therefore attributed to a significant increase in peritubular capillary reabsorption coefficient (K_r), with the mean from 0.017±0.003 to 0.030±0.005 nl/(s·mmHg). In group 2 rats, high hematocrit blood infusion led to a significant rise in APR; on average, from 10.7±0.7 to 15.0±1.2 nl/min, without changing SNGFR. This rise in APR occurred despite unfavorable changes in the physical forces, namely a significant increase in $\overline{\Delta P}_C$ and constancy in $\overline{\Delta\Pi}_C$. Instead, an increase in EABF was again associated with a significant rise in K_r (on average, from 0.016±0.002 to 0.030±0.06 nl/[s·mmHg]), which accounted entirely for the rise in APR, independently of SNGFR. In group 3 rats, in which an increase of EABF was induced pharmacologically with acetylcholine, a rise in EABF was also accompanied by a significant increase in K_r, on average, from 0.019±0.002 to 0.026±0.004 nl/(s·mmHg). The results indicate that: (*a*) K_r is modulated by EABF. (*b*) In view of plasma flow dependence of GFR, blood flow dependence of K_r and APR provides an important basis for glomerulotubular balance.

INTRODUCTION

Previous investigators have shown under a variety of experimental conditions that changes in absolute proximal fluid reabsorption rate (APR) occur in a manner predictable from simultaneously measured levels of peritubular intracapillary oncotic and hydraulic forces (1–19). Thus, reduction in the concentration of postglomerular plasma protein, induced by a variety of experimental maneuvers, such as intravenous infusion of large volume of colloid-free solutions, was associated with a decrease in APR (4, 8). Conversely, systemic or direct intraperitubular capillary infusion of hyperoncotic solutions was shown to accompany a rise in APR (4, 13, 18). In other studies, intracapillary hydraulic pressure, a force opposing peritubular capillary uptake of APR, has also been demonstrated to be an important modulator of APR (1, 3, 12, 15). However, under certain other circumstances, particularly when renal blood flow changes, the prevailing APR is not readily explainable solely on the basis of these intracapillary forces (20–27). A comparison of measurements in hydropenic and plasma-expanded rats illustrates this point: high levels

Portions of these studies were presented at the Annual Meeting of the Federations of American Societies for Experimental Biology and published in abstract form in 1983. *Kidney Int.* 23:260*a*. (Abstr.); *Fed. Proc.* 42:1090*a*. (Abstr.)

Dr. V. Kon is a recipient of the American Heart Association Clinician Scientist Award.

Received for publication 17 May 1983 and in revised form 6 July 1983.

of APR were seen in plasma-expanded rats despite levels of peritubular capillary forces that are unfavorable for avid fluid reabsorption, i.e., low oncotic or high hydraulic pressure (5, 15). Likewise, vasodilating substances, such as acetylcholine chloride (ACH) and secretin, have been shown to cause no change in APR, despite low intracapillary oncotic and high hydraulic pressure (22–24). Furthermore, in recent experiments (27), rats with congestive heart failure were characterized by a high filtration fraction (hence, high postglomerular oncotic pressure) and elevated fractional proximal reabsorption, yet APR was essentially at the same level as that of normal control rats. Under such circumstances, alternative explanations for the prevailing level of fluid reabsorption must exist in the other determinants of APR. These include alterations in interstitial oncotic and hydraulic pressures, and in the peritubular capillary reabsorption coefficient (K_r).

Therefore, to ascertain the nature of the adjustments occurring in the process of peritubular capillary fluid transfer during variations in renal blood flow, we evaluated all the factors determining uptake of APR during alterations in blood flow experimentally induced by three different maneuvers. Since glomerular hemodynamics dictate, to an important extent, the forces affecting downstream peritubular capillary fluid uptake, such as via filtration fraction, we simultaneously evaluated glomerular dynamics in this study.

GLOSSARY

ACH	acetylcholine chloride
$\overline{AP}$	mean systemic arterial pressure, *mmHg*
APR	absolute proximal fluid reabsorption rate, *nl/min*
C	protein concentration, *g/dl*
EABF	efferent arteriolar blood flow rate, *nl/min*
GBF	glomerular blood flow rate, *nl/min*
GFR	glomerular filtration rate, *ml/min*
Hct	blood hematocrit in femoral artery, *vol %*
K_f	glomerular capillary ultrafiltration coefficient, $nl/(s \cdot mmHg)$
K_r	peritubular capillary reabsorption coefficient, $nl/(s \cdot mmHg)$
P	hydraulic pressure, *mmHg*
P_r	net peritubular capillary reabsorptive pressure, *mmHg*
P_{UF}	net glomerular capillary ultrafiltration pressure, *mmHg*
ΔP	glomerular (ΔP_{GC}) or peritubular (ΔP_C) transcapillary hydraulic pressure difference ($\Delta P_{GC} = P_{GC} - P_T$; $\Delta P_C = P_C - P_I$), *mmHg*
Π	oncotic pressure, *mmHg*
$\Delta\Pi$	glomerular ($\Delta\Pi_{GC}$) or peritubular ($\Delta\Pi_C$) transcapillary oncotic pressure difference ($\Delta\Pi_{GC} \simeq \Pi_{GC}$; $\Delta\Pi_C = \Pi_C - \Pi_I$), *mmHg*
Q	plasma flow rate, *nl/min*
R	resistance to blood flow, $\times 10^{10}$ dyn·s·cm^{-5}
SNFF	single nephron filtration fraction
SNGFR	single nephron GFR, *nl/min*
$(TF/P)_{In}$	late proximal tubule fluid-to-plasma inulin concentration ratio
V_{TF}	late proximal tubule fluid flow rate, *nl/min*

Superscript

$\bar{}$	mean value

Subscripts

A	afferent arteriole
C	peritubular capillary
C^1	distalmost peritubular capillary
E	efferent arteriole (i.e., proximalmost peritubular capillary)
GC	glomerular capillary
I	cortical interstitium
T	proximal tubule

METHODS

Animal preparation and specific measurements

Studies were performed in adult male Munich-Wistar rats, weighing 223–309 g. All rats were allowed free access to tap water and standard rat chow until the day of the experiment. The animals were anesthetized with Inactin (100 mg/kg, i.p.) and placed on a temperature-regulated micropuncture table. Each animal underwent a tracheostomy. Indwelling polyethylene catheters were inserted into the right and left jugular veins for infusions of inulin and isoncotic rat plasma. The left femoral artery was catheterized for periodic sampling of blood and recording of mean systemic arterial blood pressure (AP). AP was monitored with an electronic transducer (model P-23Db, Statham Instruments Div., Gould, Inc., Oxnard, CA) connected to a direct writing recorder (model 2200, Gould, Inc.). The left kidney was exposed by ventral midline and subcostal incisions, suspended on a Lucite holder, its surface illuminated with a fiberoptic light source, and bathed with 0.9% NaCl heated to 35°–37°C.

In all experiments, micropuncture measurements and collections were carried out as follows. Timed (1–2 min) samples of fluid were collected from surface late proximal convolutions from each of one to three nephrons for determination of flow rate, inulin concentration, and calculation of tubule fluid-to-plasma inulin concentration ratio, $(TF/P)_{In}$, hence, single nephron glomerular filtration rate (SNGFR) and APR. These late surface convolutions of proximal tubules were located by observing the passage of lissamine green dye that was injected rapidly (0.05 ml of a 5% solution) into the right jugular vein catheter. The rate of fluid collection was adjusted to maintain a column of polymer oil three to four tubule diameters in length in a constant position just distal to the site of puncture. Coincident with the tubule fluid collection, femoral arterial blood samples were obtained for determination of hematocrit (Hct) and plasma inulin and protein concentrations.

Hydraulic pressures were monitored in accessible surface structures with a continuous recording, servo-null micropipette transducer system (model 3, Instrumentation for Physiology and Medicine, Inc., San Diego, CA). Micropipettes with an outer tip diameter of 1–2 μm containing 2.0 M NaCl were used. Hydraulic output from the servo-null system was coupled electronically to a second channel of a Gould recorder by means of a pressure transducer. Direct measure-

ments of time-averaged hydraulic pressures were recorded in single capillaries of surface glomeruli ($\bar{P}_{GC}$), proximal tubules (P_T), efferent arterioles (P_E), and distalmost branches of the peritubular capillaries ($P_{C'}$). By the same device, subcapsular space hydraulic pressure was also measured and values taken to represent cortical interstitial hydraulic pressure (P_I) as described in detail previously (1, 2, 20).

Protein concentrations of plasma entering glomerular (C_A) and peritubular capillaries (C_E) were determined by analyzing femoral arterial and surface efferent arteriolar blood plasmas, respectively. These inlet estimates of pre- and postglomerular plasma protein concentration also permit calculation of single nephron filtration fraction (SNFF) and initial glomerular (Q_A) and peritubular (Q_E) capillary plasma flow rates. Oncotic pressures of afferent (Π_A) and efferent (Π_E) arteriolar plasma were calculated from values of C_A and C_E, respectively. Renal lymph was obtained by inserting micropipettes (outer tip diameter of ~25 μm) into an intact renal hilar lymph vessel. Since renal lymph is thought to originate primarily in the cortex (28–31), interstitial oncotic pressure (Π_I) was estimated from the value of protein concentration of this lymph fluid. In some animals, hilar lymph vessels were not readily accessible for lymphatic fluid collection because of excessive perirenal fat tissue. In these animals, subcapsular fluid was collected for the determination of Π_I by the methods of Tucker and Blantz (3).

The volume of fluid collected from individual end-proximal tubules 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 in duplicate by the microfluorescence method of Vurek and Pegram (32). Inulin concentrations in plasma were determined by the macroanthrone method of Führ et al. (33). C_A and C_E were determined, usually in duplicate, by the fluorometric method of Viets et al. (34). Protein concentration in hilar lymph and subcapsular fluid was determined with an ultramicrocolorimeter, by means of a microadaptation (4) of the method of Lowry et al. (35).

Experimental groups

Group 1 (n = 11 rats). In this group, the effect of increased Q_A and Q_E on glomerular and postglomerular fluid transfer was simultaneously examined. The above described micropuncture measurements and collections were performed during hydropenia. After completion of this initial study period, each rat received an intravenous infusion of homologous rat plasma in a volume equal to ~3% body wt administered over 45 min. The infusion rate of plasma was then reduced to 1.2 ml/h for the remainder of the experiment. 30 min later, measurements and collections specified above were repeated. Often, recollection of late proximal tubule fluid was obtained from previous puncture sites in the same tubules studied during the initial period.

Group 2 (n = 10 rats). In this group, the protocol was designed to increase the peritubular capillary blood flow rate without altering glomerular filtration rate (GFR). In preliminary studies, the following protocol was found to fulfill these goals. The rats initially received 0.5% body wt infusion of homologous rat plasma in 15 min, followed by a reduction in the infusion rate to 1.2 ml/h for the remainder of the experiment. At the completion of the initial measurements and fluid collections specified above, each rat received an intravenous infusion of blood with a high Hct in a volume equal to ~2.5% body wt in 45 min. The infused blood was prepared as follows: On the morning of the experiment, whole blood was withdrawn from litter mates into heparinized syringes and centrifuged at 3,500 rpm for 20 min. The cells were then resuspended in saline to wash away any clots, and the suspension recentrifuged. Care was taken in preparing the erythrocytes to avoid clots, clumping, or hemolysis. The cells thus prepared were mixed with plasma and 0.9% NaCl solution in a ratio of 6:1:0.8 to attain a final Hct of ~75 vol %. After this transfusion, micropuncture measurements and collections were repeated.

Group 3 (n = 7 rats). In this group, we attempted to pharmacologically increase glomerular and postglomerular blood flow. The initial measurements were made in either hydropenic (n = 3 rats) or euvolemic conditions (n = 4 rats). The protocol for establishing euvolemic conditions has been detailed previously (36). During the second part, ACH (Sigma Chemical Co., St. Louis, MO) was infused intravenously at a rate of 2–3 μg/min. After a 30-min equilibration period, the pertinent micropuncture measurements were repeated.

Calculations

$SNGFR = (TF/P)_{In} \times V_{TF}$, where V_{TF} refers to tubule fluid flow rate. According to the Starling relationship, SNGFR is given by

$$SNGFR = K_f \times \bar{P}_{UF}$$
$$= K_f \times (\overline{\Delta P}_{GC} - \overline{\Delta \Pi}_{GC}),$$

where $\bar{P}_{UF}$ represents mean ultrafiltration pressure and $\overline{\Delta P}_{GC}$ and $\overline{\Delta \Pi}_{GC}$ are mean glomerular transcapillary hydraulic and oncotic pressure differences, respectively. Ultrafiltration coefficient (K_f), $\bar{P}_{UF}$, $\overline{\Delta P}_{GC}$, and $\overline{\Delta \Pi}_{GC}$ were calculated from equations described in detail elsewhere as were afferent (R_A) and efferent (R_E) arteriolar resistances (37). SNFF is given by $SNFF = 1 - (C_A/C_E)$. Initial glomerular plasma flow rate: $Q_A = SNGFR/SNFF$. Efferent arteriolar plasma flow rate: $Q_E = Q_A - SNGFR$. Blood flow rate per single afferent arteriole or glomerulus ($GBF = Q_A/(1 - Hct_a)$, where Hct_a, the Hct of afferent arteriolar blood, is taken to equal femoral arterial Hct. Efferent arteriolar blood flow rate ($EABF = GBF - SNGFR$.

Using the value of $(TF/P)_{In}$ and V_{TF} at the late proximal tubule, APR to the end of the proximal tubule is given by: $APR = SNGFR - V_{TF}$. The Starling relationship applied to the peritubular capillaries predicts the rate of peritubular capillary uptake of APR to be

$$APR = K_r \times \bar{P}_r$$
$$= K_r \times (\overline{\Delta \Pi}_C - \overline{\Delta P}_C)$$
$$= K_r \times [(\bar{\Pi}_C - \bar{\Pi}_I) - (\bar{P}_C - \bar{P}_I)]$$

where $\bar{P}_r$ represents mean net peritubular capillary reabsorptive pressure and $\overline{\Delta \Pi}_C$ and $\overline{\Delta P}_C$ are mean peritubular transcapillary oncotic and hydraulic pressure differences, respectively; $\bar{\Pi}_C$ and $\bar{P}_C$ are mean intracapillary oncotic and hydraulic pressures. K_r, $\bar{P}_r$, $\overline{\Delta P}_C$, $\overline{\Delta \Pi}_C$, $\bar{\Pi}_C$, and $\bar{P}_C$ were calculated from the mathematical model developed by Deen et al. (38) and Blantz and Tucker (2).

In the above described calculations for various indices of glomerular and peritubular capillary hemodynamics, Π values were estimated from the values of protein concentrations (C) with the following relationship: $\Pi = a_1C + a_2C^2$, where $a_1 = 1.63$ and $a_2 = 0.294$ (for $4 \leqq C \leqq 10$ g/dl) for plasmas, assuming an albumin-to-globulin concentration ratio of 1.0, the ratio found in normal rats by

us and others (5, 39). For renal lymph, $a_1 = 1.89$ and $a_2 = 0.469$ (for $0 \leqq C \leqq 2$ g/dl), assuming an albumin-to-globulin concentration ratio of 2.0, the ratio also found in rats (5, 39).

Statistical analyses were performed by t test where appropriate. Statistical significance was defined as $P < 0.05$.

RESULTS

Group 1 (plasma infusion). Mean values of $\overline{AP}$, the pertinent measurements of plasma composition and single nephron function during control period and after plasma infusion (group 1) are shown in Table I and Fig. 1. The initial measurements were conducted during hydropenia, i.e., without replacement of plasma volume lost during surgical preparation (36). Many of the measurements describing glomerular and peritubular capillary fluid exchanges have already been made by a number of investigators in Munich-Wistar rats under similar conditions (5, 22), and are comparable to those obtained in the present study, including the attainment of near equality between Π_E and ΔP_{GC}, as well as comparable values for $(TF/P)_{In}$ and absolute proximal tubule reabsorption rate.

After infusion of homologous rat plasma in a volume equal to ~3% body wt, $\overline{AP}$ did not change significantly, averaging 103±8 mmHg before and 110±3 mmHg after plasma infusion (Table I). As expected, the Hct decreased, from an average of 55±1 to 39±1 vol %. SNGFR increased in each animal (Fig. 1), on average from 23.2±2.4 to 45.2±3.9 nl/min. As shown in Table I, evaluation of the forces determining SNGFR revealed that ΔP_{GC} was slightly elevated after plasma infusion, averaging 33.1±0.8 vs. 34.5±0.7 mmHg. This increase in $\overline{\Delta P_{GC}}$ was associated with an elevation in both $\bar{P}_{GC}$ and P_T, as shown. Values for C_A increased on average from 5.3±0.1 to 6.0±0.1 g/dl after plasma infusion.[1] In response to plasma infusion, Q_A increased significantly and markedly, from an average of 63±5 to 210±21 nl/min. This relatively greater increase in Q_A than SNGFR in these animals is expressed as a significant fall in SNFF, the latter averaging 0.37±0.02 vs. 0.23±0.02. Lastly, K_f rose from an average of 0.063±0.011 to 0.100±0.012 nl/(s·mmHg).[2]

The average values for APR and the various factors determining postglomerular fluid uptake of APR were examined and the results also given in Fig. 1 and Table I. Although values for $(TF/P)_{In}$, an index for fractional proximal fluid reabsorption, decreased (on average from 1.98±0.09 to 1.78±0.12), APR increased uniformly and substantially (Fig. 1), averaging 10.5±1.2 nl/min before and 17.5±2.4 nl/min after plasma infusion. The hydraulic pressure measured at the beginning and distalmost accessible portions of the peritubular capillary, i.e., P_E and P_{CI}, increased with plasma infusion. Hence, the average hydraulic pressure along the peritubular capillary, $\bar{P}_C$, was 12.3±0.4 mmHg in the base-line period and rose significantly to 14.9±0.9 mmHg in the second period. Although numerically small, the increase in P_I was also significant after plasma infusion, rising from an average of 0.5±0.3 to 2.7±0.4 mmHg. As a consequence, the values for ΔP_C remained essentially unchanged (mean: 11.8±0.5 vs. 12.2±0.7 mmHg) with plasma infusion. In association with the fall in glomerular filtration fraction, the oncotic pressure measured at the beginning of the peritubular capillary, Π_E, declined after plasma infusion, on average from 35.5±1.9 to 30.9±1.2 mmHg. Nevertheless, values for oncotic pressure averaged over the entire length of the peritubular capillary, $\bar{\Pi}_C$, were virtually identical before and after plasma infusion, as shown. This near-equality in $\bar{\Pi}_C$ values between the two study periods is the result of increased peritubular capillary plasma flow rate, Q_E, after plasma infusion.[3] The increase in Q_E also served to increase the rate of blood flow entering the peritubular capillary, EABF, the latter averaging 120±11 nl/min before and 301±49 nl/min after plasma infusion. The average value for interstitial oncotic pressure, Π_I, was comparable between the two periods, also contributing to the near constancy in the value for $\Delta\Pi_C$, 22.9±0.9 mmHg before and 22.6±0.7 mmHg after plasma infusion. Overall, net peritubular capillary reabsorptive pressure, $\bar{P}_r$, was unaffected by plasma infusion, i.e., averaging 11.2±0.5 mmHg before and 10.4±0.6 mmHg after plasma. By contrast, K_r was calculated to increase in all but one rat, averaging

[1] Increase in C_A has also been observed after isoncotic plasma infusion in previous studies (14, 40). It is speculated that this increase in systemic plasma protein concentration reflects high intracapillary hydraulic pressure in peripheral capillary during plasma volume expansion, presumably causing extravasation of colloid-free fluid.

[2] The value of $\Pi_E/\Delta P_{GC}$ was <0.95 in 3 of 11 rats during hydropenia and 7 of 11 after plasma infusion. Since $\Pi_E/\Delta P_{GC}$ averaged ~1 during hydropenia, one may infer that essentially all animals were at filtration pressure equilibrium in this period and $\Pi_E/\Delta P_{GC}$ >1 or <1 in individual animals reflected technical variation. Thus, only minimum values were calculated in hydropenia, and their average given. For K_f values after plasma infusion, seven unique values were pooled with four minimum values in calculating the average. The achievement of filtration pressure equilibrium in many animals during hydropenia does not permit conclusions regarding the direction and magnitude of change in K_f, if any, occurring in these animals.

[3] The mathematical model of Deen et al. (38) predicts that the inlet value of peritubular capillary plasma flow rate determines the magnitude of dilution of plasma protein by reabsorption of colloid-free proximal tubule fluid along the peritubular capillary, hence oncotic pressure. Higher Q, for instance, by lessening the extent of dilution of plasma protein increases the average oncotic pressure.

TABLE I

Summary of Whole Body, Glomerular, and Peritubular Capillary Hemodynamics in Group 1 Rats (Plasma Infusion)

	$\overline{AP}$	Hct	C_A	SNGFR	Q_A	SNFF	$\overline{P}_{GC}$	P_T	$\overline{\Delta P}_{GC}$	R_A	R_E	K_f
	mmHg	*vol %*	*g/dl*	*nl/min*	*nl/min*		*mmHg*	*mmHg*	*mmHg*	*$\times 10^{10}$ dyn·s·cm^{-5}*		*nl/(s·mmHg)*
Before	103	55	5.3	23.2	63	0.37	45.9	12.9	33.1	3.88	2.20	>0.063
	8	1	0.1	2.4	5	0.02	0.9	0.4	0.8	0.35	0.23	0.011
After	110	39	6.0	45.2	210	0.23	48.1	13.6	34.5	1.47	0.95	0.100
	3	1	0.1	3.9	21	0.02	0.6	0.4	0.7	0.15	0.19	0.012
P	NS	<0.001	<0.005	<0.001	<0.001	<0.001	<0.01	NS	<0.05	<0.001	<0.001	NS

Values are expressed as means±1 SE. n = 11 rats.

0.017±0.003 nl/(s·mmHg) before and 0.030±0.005 nl/(s·mmHg) after plasma infusion.

Group 2. The values for SNGFR, APR, and the determinants of glomerular and peritubular capillary fluid exchanges obtained in group 2, before and after infusion of ~2.5% body wt of the high Hct blood are shown in Fig. 1 and Table II. The values for $\overline{AP}$ averaged 103±3 mmHg before and 112±5 mmHg after the blood infusion. Values for systemic arterial Hct increased uniformly, on average from 48±1 to 64±1 vol %. SNGFR was comparable between the two periods, averaging 27.3±1.7 nl/min during base-line con-

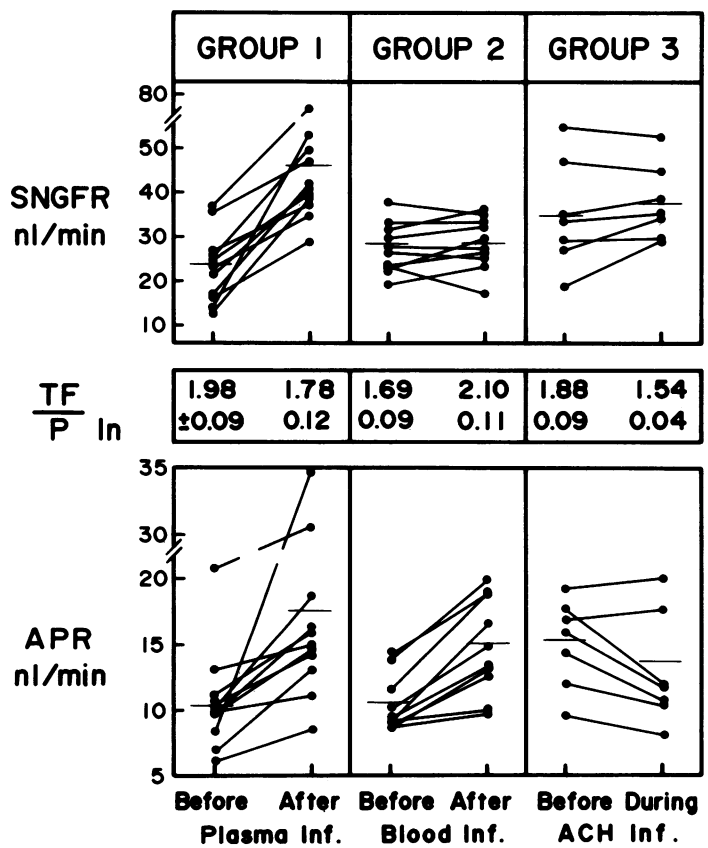

FIGURE 1 Values for SNGFR and APR measured in each animal before and after plasma infusion (*group 1*), high Hct blood infusion (*group 2*), and ACH infusion (*group 3*). Average values are given as horizontal bars. Average value for $(TF/P)_{In}$ for each group is also provided, and is expressed as mean±1 SE.

TABLE I (*Continued*)

$(TF/P)_{in}$	APR	EABF	Q_E	Π_E	$\bar{\Pi}_C$	Π_I	$\overline{\Delta\Pi_C}$	P_E	P_{C^1}	$\bar{P}_C$	P_I	$\overline{\Delta P_C}$	$\bar{P}_r$	K_r
	nl/min	*nl/min*	*nl/min*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*nl/(s·mmHg)*
1.98	10.5	120	40	35.5	27.8	4.9	22.9	16.1	8.4	12.3	0.5	11.8	11.2	0.017
0.09	1.2	11	3	1.9	1.0	0.8	0.9	0.5	0.5	0.4	0.3	0.5	0.5	0.003
1.78	17.5	301	165	30.9	27.7	5.0	22.6	18.5	11.2	14.9	2.7	12.2	10.4	0.030
0.12	2.4	49	19	1.2	0.9	0.8	0.7	0.8	0.1	0.9	0.4	0.7	0.6	0.005
NS	<0.01	<0.005	<0.001	<0.025	NS	NS	NS	<0.05	<0.025	<0.025	<0.001	NS	NS	<0.025

ditions and 28.5±1.9 nl/min after high Hct blood infusion. Of the various determinants of SNGFR, ΔP_{GC} failed to change significantly, averaging 32.8±0.8 mmHg in the first period and 33.0±1.0 mmHg in the second period. The constancy in ΔP_{GC} reflected an absence of changes in both $\bar{P}_{GC}$ and P_T throughout this experiment, averaging 45.4±0.8 vs. 45.7±0.9 mmHg and 12.6±0.4 vs. 12.7±0.3 mmHg, respectively. As in group 1 experiments, C_A increased mildly and significantly after blood infusion. Values for Q_A also increased slightly in response to blood infusion as shown in Table II. Finally, the mean values for K_f increased from an average value of 0.059±0.005 to 0.085±0.008 nl/(s·mmHg).[4]

In contrast to the observed constancy in SNGFR, values for APR increased significantly from an average of 10.7±0.7 to 15.0±1.2 nl/min after blood infusion (Fig. 1, Table II). Thus, the $(TF/P)_{In}$ also increased significantly from a mean of 1.69±0.09 to 2.10±0.11. The various factors determining postglomerular fluid exchange are also given in Table II. Infusion of high Hct solution caused a uniform increase in P_E and P_{C^1}, yielding a significantly higher $\bar{P}_C$ in the second period (mean 12.4±0.4 vs. 15.4±0.6 mmHg). Quantitatively, this increase in $\bar{P}_C$ exceeded a small but significant increase in P_I and led to a higher value for $\overline{\Delta P_C}$ after blood infusion, the latter averaging 11.2±0.3 mmHg before and 13.3±0.5 mmHg after infusion. In contrast, Π_E and $\bar{\Pi}_C$ remained relatively constant before and after blood infusion. Although there was a small but significant increase in Π_I in the second period of these experiments (Table II), values for $\overline{\Delta\Pi_C}$ were comparable between the two periods, averaging 23.7±1.5 vs. 24.1±1.6 mmHg. Owing to the increase in the level of $\overline{\Delta P_C}$ and the constancy in $\overline{\Delta\Pi_C}$, average value for $\bar{P}_r$ was calculated to decrease numerically although this decrease did not reach statistical significance, as shown. K_r increased in all but one animal, averaging 0.016±0.002 nl/(s·mmHg) before and 0.030±0.006 nl/(s·mmHg) after blood infusion. In association with the increased Hct of systemic blood and a very mild increase in Q_E (59±8 vs. 71±9 nl/min), EABF increased significantly and substantially, on average from 141±14 vs. 252±31 nl/min.

Group 3. The above measurements were duplicated in group 3, before and during intravenous infusion of ACH and the results are given in Fig. 1 and Table III. AP fell slightly, on average from 106±2 to 100±3 mmHg. Hct was identical before and after ACH infusion, averaging 51±2 vol % for both periods. Values for SNGFR failed to change significantly (35.0±4.5 vs. 38.0±3.1 nl/min). ΔP_{GC} increased significantly in response to ACH infusion, averaging 35.6±1.5 mmHg before and 38.4±1.6 mmHg during the infusion. These values reflect a slight increase in $\bar{P}_{GC}$ (49.2±1.4 to 52.0±1.5 mmHg) and constancy in P_T (13.5±1.3 vs. 13.6±0.7 mmHg). Whereas C_A failed to change significantly with ACH infusion, Q_A increased markedly and significantly, from an average of 111±17 to 148±20 nl/min. This rise in Q_A with relatively constant SNGFR is expressed by a fall in the value for SNFF, which averaged 0.32±0.01 before and 0.27±0.02 during ACH infusion. Values for K_f fell on average from 0.076±0.019 to 0.059±0.018 nl/(s·mmHg),[5] but this change failed to reach statistical significance. Thus, the constancy in the value of SNGFR during ACH infusion occurred under the opposing influences of increases in Q_A and ΔP_{GC} vs. a decrease in K_f.

In these animals, values for APR also failed to change significantly, averaging 15.4±1.3 nl/min before and

[4] For reasons identical to those of group 1 hydropenic rats (footnote 2), only minimum values were calculated for both experimental periods in this group. Thus, the values given here represent average for minimum K_f values, and conclusions regarding changes in K_f values cannot be determined.

[5] The value for $\Pi_E/\overline{\Delta P_{GC}}$ was >0.95 in three of seven animals before ACH infusion, where only minimum values were calculated. These minimum values were pooled with unique values from four animals for calculation of the average. $\Pi_E/\overline{\Delta P_{GC}}$ was <0.95 in all of the animals during ACH infusion, permitting calculation of unique values for K_f for this period.

TABLE II

Summary of Whole Body, Glomerular, and Peritubular Capillary Hemodynamics in Group 2 Rats (Blood Infusion)

	$\overline{AP}$	Hct	C_A	SNGFR	Q_A	SNFF	$\bar{P}_{GC}$	P_T	$\overline{\Delta P}_{GC}$	R_A	R_E	K_f
	mmHg	*vol %*	*g/dl*	*nl/min*	*nl/min*		*mmHg*	*mmHg*	*mmHg*	*×10¹⁰ dyn·s·cm⁻⁵*		*nl/(s·mmHg)*
Before	103	48	5.5	27.3	87	0.32	45.4	12.6	32.8	2.76	1.68	>0.059
	3	1	0.2	1.7	9	0.02	0.8	0.4	0.8	0.21	0.15	0.005
After	112	64	6.0	28.5	100	0.29	45.7	12.7	33.0	1.88	0.84	>0.085
	5	1	0.2	1.9	10	0.02	0.9	0.3	1.0	0.12	0.10	0.008
P	NS	<0.001	<0.005	NS	<0.025	<0.05	NS	NS	NS	<0.001	<0.001	<0.025

Values are expressed as means±1 SE. n = 10 rats.

13.3±1.7 nl/min after ACH infusion, while values for $(TF/P)_{In}$ decreased from an average of 1.88±0.09 to 1.54±0.04 (Fig. 1, Table III). The measurements of the forces affecting peritubular capillary uptake of APR revealed that P_E, P_{C^1}, and hence $\bar{P}_C$ increased substantially, the latter averaging 12.9±0.9 vs. 17.2±0.7 mmHg. As in group 2, although the P_I also increased significantly, the increase in $\bar{P}_C$ exceeded that of P_I and yielded higher ΔP_C value, averaging 11.5±0.9 mmHg before and 14.4±0.5 mmHg after ACH infusion. Similar to group 1 animals, SNFF fell during ACH, reflecting relatively greater increase in Q_A than SNGFR, causing decreased Π_E values during ACH infusion, on average from 34.4±0.4 to 29.7±0.9 mmHg. In association with an increase in Q_E, however, values for $\bar{\Pi}_C$ remained essentially constant during ACH, as shown (38). This increase in Q_E was also associated with an increase in EABF (mean 193±20 vs. 266±26 nl/min). Values for Π_I were also comparable between the two periods. Consequently, $\Delta\Pi_C$ remained equivalent before and after ACH infusion, as shown. The sum of the increased ΔP_C and similar $\Delta\Pi_C$ comprised a reduction in values for $\bar{P}_r$, averaging 14.2±1.3 mmHg in the first vs. 9.7±1.4 mmHg in the second study period. There was a mild but significant increase in values for K_r from an average of 0.019±0.002 nl/(s·mmHg) before to 0.026±0.004 nl/(s·mmHg) after ACH infusion.

DISCUSSION

In response to isoncotic plasma infusion, SNGFR increased twofold. Of the four glomerular microcirculatory indices determining SNGFR, ΔP_{GC} increased by ~1 mmHg and this slight increase is expected to contribute little to the observed marked increase in SNGFR. Statistical comparison was not possible for K_f values between the two periods, because of the filtration pressure equilibrium achieved in hydropenia. However, average minimum K_f value during hydropenia was nearly 60% that after plasma infusion, indicating that, even if K_f did increase (by a maximum of 40% of the postplasma infusion level), the influence of this degree of increase in K_f on the final value of SNGFR was

TABLE III

Summary of Whole Body, Glomerular, and Peritubular Capillary Hemodynamics in Group 3 Rats (ACH)

	$\overline{AP}$	Hct	C_A	SNGFR	Q_A	SNFF	$\bar{P}_{GC}$	P_T	$\overline{\Delta P}_{GC}$	R_A	R_E	K_f
	mmHg	*vol %*	*g/dl*	*nl/min*	*nl/min*		*mmHg*	*mmHg*	*mmHg*	*×10¹⁰ dyn·s·cm⁻⁵*		*nl/(s·mmHg)*
Before	106	51	5.7	35.0	111	0.32	49.2	13.5	35.6	2.34	1.60	0.076
	2	2	0.1	4.5	17	0.01	1.4	1.3	1.5	0.19	0.20	0.019
After	100	51	5.6	38.0	148	0.27	52.0	13.6	38.4	1.44	1.14	0.059
	3	2	0.1	3.1	20	0.02	1.5	0.7	1.6	0.10	0.13	0.018
P	<0.025	NS	NS	NS	<0.005	<0.01	<0.025	NS	NS	<0.005	<0.01	NS

Values are expressed as means±1 SE. n = 7 rats.

TABLE II (*Continued*)

$(TF/P)_{in}$	APR	EABF	Q_E	Π_E	$\bar{\Pi}_C$	Π_I	$\overline{\Delta\Pi_C}$	P_E	P_{C^1}	$\bar{P}_C$	P_I	$\overline{\Delta P_C}$	$\bar{P}_r$	K_r
	nl/min	*nl/min*	*nl/min*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*nl/(s·mmHg)*
1.69	10.7	141	59	33.5	28.2	4.5	23.7	16.7	8.1	12.4	1.2	11.2	12.5	0.016
0.09	0.7	14	8	2.2	1.7	0.4	1.5	0.5	0.6	0.4	0.2	0.3	1.5	0.002
2.10	15.0	252	71	35.1	29.1	5.0	24.1	20.1	10.7	15.4	2.1	13.3	10.7	0.030
0.11	1.2	31	9	1.9	1.4	0.5	1.6	0.7	0.7	0.6	0.2	0.5	1.7	0.006
<0.01	<0.001	<0.001	<0.01	NS	NS	<0.001	NS	<0.001	<0.001	<0.001	<0.01	<0.001	NS	<0.025

rather small.[6] Instead, glomerular plasma flow rate increased twofold after plasma infusion, and we conclude, as others have previously, that it is this increase in Q_A that was primarily responsible for the increased SNGFR.

After plasma infusion, APR also increased. Our evaluation of various forces influencing the peritubular capillary uptake of APR revealed that there was a uniform and comparable increase in both intracapillary and interstitial hydraulic pressures after plasma expansion, so that $\overline{\Delta P_C}$ remained unaffected. SNFF declined with plasma infusion, and oncotic pressure at the beginning of the peritubular capillary was lower after plasma infusion. However, when this value was averaged over the entire length of the peritubular capillary, a difference in $\bar{\Pi}_C$ between the two periods was undetectable (38). Since Π_I were also comparable before and after plasma infusion, $\overline{\Delta\Pi_C}$ was unaffected. Therefore, as with $\overline{\Delta P_C}$, $\overline{\Delta\Pi_C}$ fails to explain the observed increase in APR after plasma infusion. These assessments of the peritubular transcapillary forces led to the inevitable conclusion that the last determinant of APR, K_r, increased after plasma infusion. Indeed, values for K_r were calculated to increase significantly and substantially after plasma infusion.

In these experiments, a strong correlation was demonstrated between the level of EABF and the value of K_r. In addition to this relationship between EABF vs. K_r and APR, there was a positive correlation between SNGFR and APR. Since fluid load to the proximal tubule is regarded, at least under certain circumstances (41, 42), to be important in modulating the rate of reabsorption by the proximal tubule, we designed the second set of experiments aiming to increase EABF while maintaining SNGFR constant. Our goal was to examine if an increase in K_r, provided it occurred, can

[6] On the basis of the minimum K_f values obtained before and unique K_f values after plasma infusion, it was possible to estimate the maximum extent to which a change in K_f, if it occurred, may have contributed to the observed increase in SNGFR. To estimate such an increase, theoretical value for SNGFR was calculated on the assumption that after plasma infusion K_f remained at the minimum estimated level of hydropenia while the other determinants changed to the observed levels. SNGFR value thus calculated was 38.6 nl/min, a value quite comparable to the observed value (45.2 nl/min), indicating that even if a maximal increase in K_f occurred, it had little causal role in the increased SNGFR after plasma infusion. By contrast, when Q_A was assumed not to have increased with plasma infusion, SNGFR is predicted to remain essentially at the hydropenic level (17.8 nl/min vs. 23.2 nl/min).

TABLE III (*Continued*)

$(TF/P)_{in}$	APR	EABF	Q_E	Π_E	$\bar{\Pi}_C$	Π_I	$\overline{\Delta\Pi_C}$	P_E	P_{C^1}	$\bar{P}_C$	P_I	$\overline{\Delta P_C}$	$\bar{P}_r$	K_r
	nl/min	*nl/min*	*nl/min*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*nl/(s·mmHg)*
1.88	15.4	193	76	34.4	28.4	2.7	25.7	16.8	9.1	12.9	1.5	11.5	14.2	0.019
0.09	1.3	20	13	0.4	1.2	0.4	0.7	1.2	0.6	0.9	0.2	0.9	1.3	0.002
1.54	13.3	266	110	29.7	27.4	3.3	24.1	20.7	13.7	17.2	2.8	14.4	9.7	0.026
0.04	1.7	26	17	0.9	2.3	0.3	1.1	1.1	0.5	0.7	0.5	0.5	1.4	0.004
<0.05	NS	<0.005	<0.005	<0.005	NS	NS	NS	<0.001	<0.005	<0.001	<0.025	<0.005	<0.005	<0.05

lead to an increase in APR, independently of changes in filtration rate. While our protocol proved successful in increasing EABF by maintaining the SNGFR constant, it led to a substantial increase in APR. Evaluation of forces influencing peritubular capillary uptake of APR showed that this increase in APR occurred despite unfavorable changes in the peritubular transcapillary Starling forces, i.e., increased $\overline{\Delta P_C}$ and constant $\overline{\Delta \Pi_C}$. Again, a marked rise in reabsorption coefficient was implicated in effecting this increase in fluid reabsorption. It is noteworthy that this increase in K_r and APR during increased EABF occurred in the absence of changes in glomerular filtration.

To examine further the relationship between EABF and K_r, we performed a third set of experiments, using a vasodilator, ACH, to pharmacologically induce an increase in EABF. The ACH infusion failed to affect the value for SNGFR. Of the individual determinants of SNGFR, ΔP_{GC} and Π_A remained unchanged throughout this experiment. Instead, it was shown that the near constancy in SNGFR was largely a result of opposing influences of increased Q_A and decreased K_f during ACH infusion.

Although these changes in glomerular hemodynamics after ACH infusion did not produce a net change in SNGFR, they had a profound effect on the downstream peritubular capillary forces. The hydraulic pressure in the postglomerular vessels increased markedly and greatly exceeded the concomitant increase in P_I. Therefore, as in the blood-infused animals, $\overline{\Delta P_C}$ increased markedly. While the decrease in K_f and the profound increase in Q_A during ACH infusion led to a reduction in immediate postglomerular plasma protein concentration, the higher Q_E resulted in comparable values for average intracapillary oncotic pressures before and during ACH infusion (38). Since Π_I also remained virtually constant, $\overline{\Delta \Pi_C}$ values were unaffected by ACH. The observed increase in $\overline{\Delta P_C}$ and constancy in $\overline{\Delta \Pi_C}$ during ACH infusion are expected to favor a decline in APR. Yet, the measured values for APR were similar before and after ACH infusion, again implicating an increase of K_r during ACH-induced increase in EABF.[7] Overall, as shown in Fig. 2, a strong positive correlation between EABF and K_r was demonstrated in all three groups studied, where EABF changes were induced by different experimental maneuvers.

Several previous studies have shown that changes in K_r can occur under various circumstances and are capable of influencing APR (3, 16, 23, 25, 26, 43). These changes in K_r were usually observed in association with variation in renal blood flow.[8] Mertz et al. (23) have recently shown that secretin-induced renal vasodilation and increase in renal blood flow was accompanied by a marked increase in K_r. In our recent study, progressive increases in the reabsorption rate and renal blood flow in growing rats were shown to accompany a rise in K_r (25). In another micropuncture study (26), renal nerve stimulation in rats was found to depress K_r in association with a tendency of EABF to fall. A study of whole kidney clearance of macromolecules in dogs by Whiteside and Silverman (43) concluded that, at least for a certain range of renal blood flow, the peritubular capillary permeability coefficient changes in strong relation with postglomerular blood flow.

Since K_r is a product of both the permeability of the capillary wall to water and the surface area available for fluid exchange, changes in either or both of these terms can account for the observed EABF-dependence of K_r. In this regard, studies in vascular systems of other organs demonstrated that blood flow rate is an important determinant of capillary surface area. For example, in skeletal muscle, the increase in blood flow associated with exercise accompanies increasing number of open vascular channels (46), whereas nerve stimulation decreases the number of these channels, thereby affecting the blood flow and the rate of transfer of solutes and water (46). Although most of such studies emphasize the number of open capillary channels available for fluid transfer as an effector mechanism for blood flow dependency of permeability coefficient, another possibility exists, namely that the diameter of the already patent vascular channels may vary in accordance with the level of inflow. In this respect, Koch Jensen and Steven (47, 48) demonstrated by a morphometric method that the diameter of the peritubular capillary in renal superficial cortex can indeed change in response

[7] Divergent effects of ACH upon K_f in the glomerular capillary bed and K_r in the peritubular capillary bed may be related to anatomical differences between these two vascular beds. The decrease in K_f value during ACH infusion, at least numerically, may be mediated through the mesangial cells in the glomerulus. The apparent absence of their response in the peritubular capillary may be related to lack of these contractile elements in the postglomerular circulation.

[8] On the basis of previous (1, 15) and present experimental data, it seems clear that other factors must also be contributory in determining the level of K_r. For instance, in other vascular systems (44, 45), intracapillary pressure also appears to affect permeability coefficient or surface area of the capillary. Available data further indicate that the relationship between renal blood flow and K_r may be nonlinear, since increases in blood flow from mildly to modestly high level was not accompanied by detectable changes in K_r (1, 15).

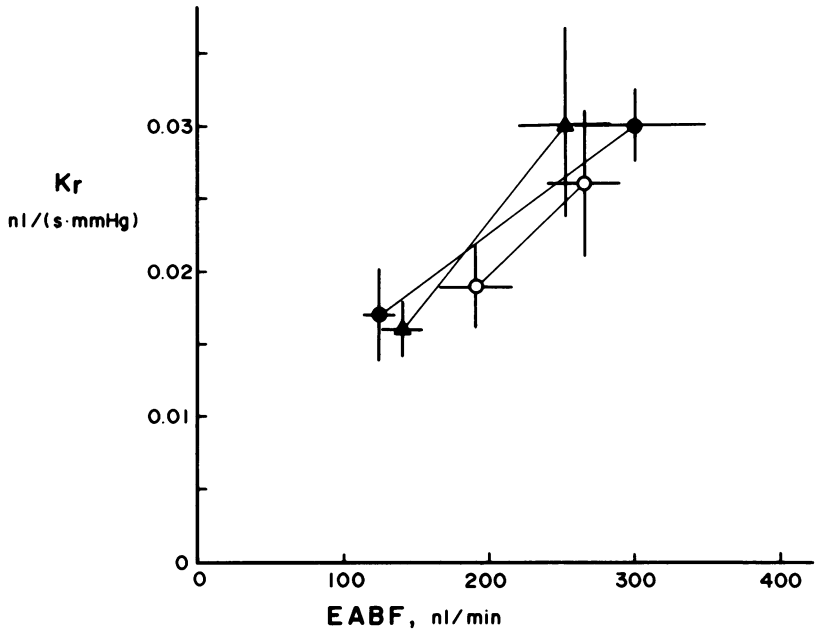

FIGURE 2 Summary of the data for EABF and K_r obtained in the three groups of rats studied. Data obtained within the same group of animals are connected by straight lines. Plasma infusion (●); blood infusion (▲); ACH infusion (○).

to certain experimental maneuvers. Thus, it is possible that variation in the renal blood flow can affect the peritubular capillary coefficient by passively changing the surface area available for reabsorption through opening of new channels, expanding already patent ones, or a combination thereof. It is also conceivable that when such expansion of capillaries occurs, the permeability of the capillary wall to water also increases to some extent. In all three groups of animals examined in the present study, the resistances of the peritubular capillary to axial flow decreased uniformly; on average, from 0.53 ± 0.09 to $0.23\pm0.04 \times 10^{10}$ $dyn \cdot s \cdot cm^{-5}$ after plasma infusion; 0.52 ± 0.07 to $0.33\pm0.05 \times 10^{10}$ $dyn \cdot s \cdot cm^{-5}$ after blood infusion; and 0.33 ± 0.04 to $0.21\pm0.03 \times 10^{10}$ $dyn \cdot s \cdot cm^{-5}$ during ACH infusion. This uniform decline in resistances suggests that the observed increase in K_r in each of these instances was, at least in part, related to an increase in capillary diameter and/or to recruitment of new capillary channels, and hence, surface area available for reabsorption.

It should be recognized that our observations are also consistent with the possibility that the prevailing circulatory volume status may, through activation (or deactivation) of systemic and/or local factors, directly influence K_r. Volume expansion or administration of vasodilators may, via increased circulatory vasodilative substances (or decreased vasoconstrictive substances), affect both the renal blood flow and K_r.

The observed blood flow dependence of APR is reminiscent of plasma flow dependence of GFR in this species of animals and lead us to consider that this EABF dependence of K_r may play an important role in the so-called glomerulotubular balance, a term used to describe changes in GFR that are accompanied by directionally similar and roughly proportional changes in the rate of fluid reabsorbed by the proximal tubule. Fig. 3 illustrates this point. The open and filled circles in the bottom left corner of the figure depict typical values for SNGFR and APR in normal rats. The ratio between APR and SNGFR defines fractional proximal reabsorption. Any point falling on the dashed straight line, therefore, indicates maintenance of perfect glomerulotubular balance. In the first group of animals, we have shown, as have others (36, 49, 50), that, after isoncotic plasma infusion, increase in SNGFR occurs, owing primarily to increased plasma flow rate, as indicated by the rightward arrow. Concomitantly, the rise in plasma flow brought about an increase in EABF and the associated increase in K_r, which in turn led to an increase in APR, indicated by the upgoing arrow directed toward (but not reaching) the line of perfect glomerulotubular balance. In the second group of animals, the selective increase in EABF with high Hct

blood infusion caused an increase in APR without changes in SNGFR, as indicated by the left upgoing arrow, i.e., away from the line of perfect glomerulotubular balance. We believe that under physiologic and pathophysiologic circumstances SNGFR and APR change in a manner best described by a point falling between the two experimentally induced extremes shown in Fig. 3, i.e., more perfect glomerulotubular balance (interrupted lines). This is because physiologic variation in renal blood flow is not a consequence of changes in the flow of either plasma or erythrocytes alone, but is instead a combination of the two.

Thus, this blood flow dependence of K_r and APR, together with plasma flow dependence of GFR, provide a physiologic basis of glomerulotubular balance, particularly when GFR varies along with alterations in renal blood flow. On the other hand, when changes in GFR occur in the absence of changes in renal blood flow, peritubular capillary physical forces become important in the preservation of glomerulotubular balance, i.e., via filtration fraction and oncotic pressure. Clearly, our observations do not negate the importance of luminal or epithelial factors (41, 42, 51, 52) that might also contribute to the phenomenon of glomerulotubular balance. Instead, it is more likely that multiple mechanisms are necessary for the effective achievement of glomerulotubular balance, with the combination of physical forces and K_r being an integral component.

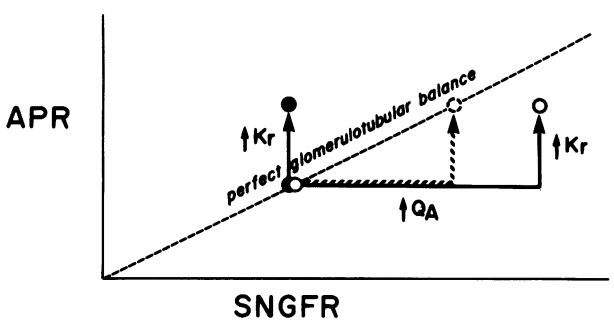

FIGURE 3 Schematic presentation of the proposed mechanism for the preservation of glomerulotubular balance when SNGFR varies with renal blood flow. The two arrows with solid lines depict changes during two extreme experimental perturbations (plasma infusion [O] on the *right* and high Hct blood infusion [●] on the *left*). In contrast to these two experimental circumstances, where glomerulotubular balance is disrupted owing to preferential increase in the flow of plasma or erythrocyte component, it is predicted that physiological circumstances are characterized by a more perfect balance (interrupted line). Thus, GFR changes in accord with Q_A, while greater changes in K_r and APR occur than are expected from the degree of increase in plasma flow alone. It is the simultaneous increase in the flow of erythrocytes component that augments these changes in K_r and APR.

ACKNOWLEDGMENTS

We would like to express our appreciation to Miss Sheila L. Ellis for her expert technical assistance.

This work was supported, in part, by National Institutes of Health grants AM 27853 and AM 16392.

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