The Dynamics of Glomerular Ultrafiltration in the Rat

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ABSTRACT Using a unique strain of Wistar rats endowed with glomeruli situated directly on the renal cortical surface, we measured glomerular capillary pressures using servo-nulling micropipette transducer techniques. Pressures in 12 glomerular capillaries from 7 rats averaged 60 cm H_2O, or approximately 50% of mean systemic arterial values. Wave form characteristics for these glomerular capillaries were found to be remarkably similar to those of the central aorta. From similarly direct estimates of hydrostatic pressures in proximal tubules, and colloid osmotic pressures in systemic and efferent arteriolar plasmas, the net driving force for ultrafiltration was calculated. The average value of 14 cm H_2O is lower by some two-thirds than the majority of estimates reported previously based on indirect techniques. Single nephron GFR (glomerular filtration rate) was also measured in these rats, thereby permitting calculation of the glomerular capillary ultrafiltration coefficient. The average value of 0.044 nl sec^{-1} cm H_2O^{-1} $glomerulus^{-1}$ is at least fourfold greater than previous estimates derived from indirect observations.

INTRODUCTION

More than a century ago, Ludwig proposed that the initial event in the process of urine formation is the production of an ultrafiltrate of plasma across the glomerular capillary wall (1). Refinement of this view by Starling (2) to indicate that the mechanisms responsible for this ultrafiltrate formation are the same as those governing the movement of fluid across capillary membranes generally (namely the magnitude and direction of the imbalance of hydrostatic and colloid osmotic pressures across capillary walls) has to date received direct experimental confirmation only in nonmammalian species (3–5). That similar direct measurements have thus far not been performed in mammalian glomerular capillaries is due largely to the fact that glomeruli are rarely present as surface structures and are not therefore accessible for direct study. Recently however, a strain of Wistar rats with glomeruli situated on the renal surface has been identified in the laboratory of Dr. Klaus Thurau of the University of Munich. Using these rats[1] we have undertaken in the present study to characterize the transcapillary forces governing the formation of glomerular ultrafiltrate in the mammalian kidney.

METHODS

Studies were performed on seven normally hydropenic rats (six adults and one young rat) which were allowed free access to food and water. They were anesthetized with Inactin (100 mg/kg) and prepared for micropuncture as described previously (6).

Pressure measurements were obtained in capillaries of 12 different glomeruli, using continuous recording servo-nulling micropipette transducer techniques (7–9). Micropipettes with outer tip diameters of 2–3 μ and containing 1.5 M NaCl were used. Penetration of Bowman's Space and entry into single glomerular capillaries was performed under stereomicroscopic control (× 210). Hydraulic output from the servo-system was channeled via a strain gauge to a recorder. Accuracy, frequency response, and stability features of this servo-system will be described in detail elsewhere (Brenner et al. submitted for publication). In addition to glomerular capillary hydrostatic pressures ($\bar{P}_{GC}$)[2], we also recorded pressures in Bowman's capsule (P_{BS}), and in separate adjacent proximal tubules (P_T), efferent arterioles (P_{EA}) and third order branch peritubular capillaries (P_C) in each rat.

To obtain similarly direct estimates of mean glomerular capillary colloid osmotic pressure ($\bar{\pi}_{GC}$), protein concentrations in femoral arterial and efferent arteriolar blood plasmas were measured as recently described (6). Colloid osmotic pressures (COP) were calculated using the expression of Landis and Pappenheimer (10). $\bar{\pi}_{GC}$ then was taken as one-half the sum of the calculated COP at each site. For estimation of the ultrafiltration coefficient (K_f) for glomerular capillaries, single

This work was presented in part at the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J., 1 May 1971.

Received for publication 10 May 1971.

[1] The generous gift to us of a number of adult rats of this unique strain by Professor Thurau is gratefully acknowledged.

[2] *Abbreviations used in this paper:* $\overline{AP}$, mean arterial pressure; COP, colloid osmotic pressure; K_f, ultrafiltration coefficient; P_{BS}, Bowman's Space pressure; P_C, peritubular capillary pressure; P_{EA}, efferent arteriolar pressure; $\bar{P}_{GC}$, mean glomerular capillary hydrostatic pressure; P_T, proximal tubule pressure; P_{UF}, net glomerular ultrafiltration pressure; $\bar{\pi}_{GC}$, mean glomerular capillary colloid osmotic pressure; π_{TF}, tubule fluid colloid osmotic pressure; SNGFR, single nephron glomerular filtration rates.

TABLE I

A Summary of the Measured Determinants of Glomerular Ultrafiltration in Seven Munich-Wistar Rats

Rat No.	Body wt	Kidney wt	Obs. No.	$\overline{AP}$[a]	P_T[b]	P_{BS}[c]	$\bar{P}_{GC}$[d]	[Protein][e] F.A.	[Protein][e] E.A.	π_{FA}	π_{EA}[f]	$\bar{\pi}_{GC}$[g]	P_{UF}[h]	SNGFR[i]	K_f[j]
	(g)	(g)		*cm H_2O*	*cm H_2O*	*cm H_2O*	*cm H_2O*	*g/100 ml*		*cm H_2O*		*cm H_2O*		*nl/sec*	*nl/sec/ cm H_2O/ glom*
1	298	1.02	1	122	14.5	13	78	5.8	7.8	26.1	41.2	33.7	29.8	0.54	0.019
			2											0.55	
2	290	1.00	1	135	11	12	55	5.4	8.1	23.6	43.7	33.6	11.9	0.56	0.047
			2	142	8	8	55							0.56	
			3			10									
3	308	1.22	1	110	11	10	65	5.4	9.2	23.6	54.0	38.8	15.2	0.42	0.031
			2											0.51	
4	123	0.61	1	108	13	16	60	5.2	8.0	22.3	42.8	32.5	14.0	0.32	0.023
			2	110		10	56							0.35	
			3	110		10	64								
			4	110		12.5	60								
			5	110			57.5								
5	250	1.08	1	162		15		5.3	7.0	23.0	34.7	28.8	9.2	0.50	0.050
			2	162		10								0.42	
			3	162		10									
			4	156	11	10	49								
6	290	1.51	1	108	10	10	62	6.0	9.3	27.4	55.0	41.2	10.8	0.44	0.042
			2											0.47	
7	252	0.92	1	160	14	13	60	5.2	9.3	22.8	55.0	38.9	7.1	0.77	0.098
			2											0.62	
Mean					11.6	11.3	60.1	5.5	8.4	24.1	46.6	35.4	14.0	0.46	0.044
±1 SE					0.8	0.6	2.1	0.1	0.3	0.7	3.0	1.7	2.8	0.06	0.010

a, mean arterial pressure; b, proximal tubule pressure; c, Bowman's Space pressure; d, mean glomerular capillary hydrostatic pressure; e, protein concentration in femoral arterial and efferent arteriolar blood plasmas; f, colloid osmotic pressures, calculated for values shown at e, using the Landis-Pappenheimer equation (10); g, mean glomerular capillary colloid osmotic pressure, calculated as $\frac{\pi_{FA} + \pi_{EA}}{2}$; h, net ultrafiltration pressure, calculated as $\bar{P}_{GC} - P_T - \bar{\pi}_{GC}$; i, single nephron glomerular filtration rate; j, ultrafiltration coefficient for these glomerular capillaries.

nephron glomerular filtration rates (SNGFR) also were measured in these rats, using free-flow micropuncture techniques. Standard analytical methods were employed (6).

RESULTS

Pressures were measured in single capillaries of 12 superficial glomeruli from 7 normal Munich–Wistar rats (Table I). Values for $\bar{P}_{GC}$ ranged from 49 to 78 cm H_2O, with 10 of 12 pressures being between 55–65 cm H_2O. As shown in Fig. 1 the wave form profile of the glomerular capillary pressure pulse is very similar to that of the central aorta. This preservation of the aortic wave form in these small diameter vessels makes it likely that their walls are relatively rigid. As shown in Fig. 2, the major changes in intrarenal vascular pressure occurred on either side of the glomerular capillary bed. An average fall in mean systemic arterial pressure ($\overline{AP}$) of 51% occurred to the glomerular capillary. A second large pressure differential occurred between glomerular capillaries and surface efferent arterioles. Beyond the latter site the falls in pressure were small and gradual.

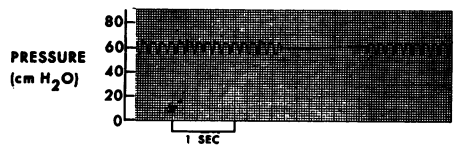

FIGURE 1 Characteristic pressure pattern in a surface glomerular capillary. Mean pressure is given by the horizontal line.

The relationship between the rate of formation of glomerular ultrafiltrate (GFR) and the responsible driving forces is given by the expression:

$$GFR = K_f(\bar{P}_{GC} - P_T - \bar{\pi}_{GC} + \pi_{TF}) \quad [1]$$

where K_f represents the ultrafiltration coefficient (ie, hydraulic conductivity per unit area × glomerular capillary surface area), $\bar{P}_{GC}$, P_T, and $\bar{\pi}_{GC}$ are as defined above, and π_{TF} tubule fluid COP. Values for π_{TF} are very close to zero and may therefore be neglected.[3]

[3] Direct measurements of protein concentration in fluid from Bowman's Space of five glomeruli in four Munich–Wistar rats not otherwise studied yielded values below 200 mg/100 ml. The mean estimate of COP was 0.4 cm H_2O.

The net driving force for glomerular ultrafiltration (P_{UF}) is given then by the expression:

$$P_{UF} = \bar{P}_{GC} - P_T - \bar{\pi}_{GC} \quad [2]$$

Directly measured estimates of each term for each rat are summarized in Table I. 15 measurements of pressure in Bowman's space were obtained and averaged 11.3 cm H_2O. Pressures recorded in proximal tubules of these same rats were similar averaging 11.6 cm H_2O. Protein concentrations in systemic and efferent arteriolar plasmas averaged 5.5 and 8.4 g/100 ml respectively, yielding an average superficial cortical filtration fraction of 0.35.[4] Using the Landis-Pappenheimer equation (10), COP in efferent arterioles was calculated to average 46.6 cm H_2O. $\bar{\pi}_{GC}$ ranged from 28.8 to 41.2 cm H_2O and averaged 35.4 cm H_2O. Values for P_{UF} were therefore relatively low, ranging below 16 cm H_2O in all but one rat; for all an average value of 14.0 cm H_2O ±2.8 SE was obtained.

As shown in Table I, SNGFR was measured in each of two proximal tubules in each rat. K_f expressed as nl sec^{-1} cm H_2O^{-1} driving force averaged 0.044 per glomerulus.

DISCUSSION

Values for each index of superficial cortical nephron and microvascular function measured in the Munich-Wistar rats in the present study (SNGFR, $\overline{\Delta P}$, P_T, P_{EA}, and P_C, and cortical filtration fractions) were quantitatively similar to values observed in the adult Sprague-Dawley rat (6, 8, 9). Accordingly, it seems reasonable to assume that the values for $\bar{P}_{GC}$, P_{BS}, P_{UF}, and K_f obtained in the present study are likely to be representative of values for the more commonly studied Sprague-Dawley rat but which to date have eluded direct measurement. Attempts to estimate P_{UF} and $\bar{P}_{GC}$ by indirect means (single nephron and whole kidney stop flow studies) in both strains of rats have been reported (11–14). The assumption common to each of these latter studies is that these methods for elevation of P_T permit encroachment on the value for $\bar{P}_{GC}$ without significantly disturbing it. Since reported estimates of $\bar{P}_{GC}$ using these stop-flow techniques in the rat have been higher than 80 cm H_2O (11–14), often in excess of 100 cm H_2O, and therefore much higher than values measured directly in the present study, this assumption may be invalid. In all liklihood, autoregulatory adjustments are initiated in response to progressive elevations in P_T and result in compensatory parallel elevations in $\bar{P}_{GC}$, perhaps secondary to dilation of afferent arterioles.[5] From these high estimates of $\bar{P}_{GC}$, calculated values for P_{UF} have generally been in the range of 50 cm H_2O, again far greater than that actually measured in the present study

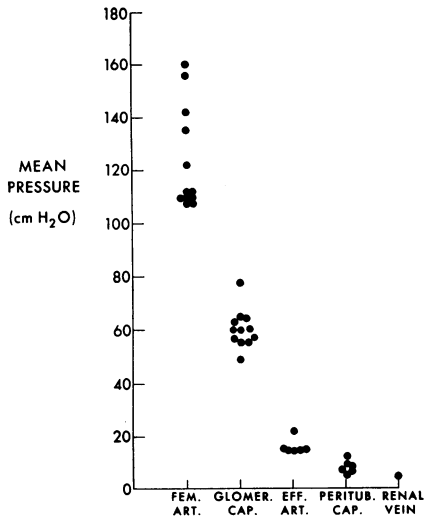

FIGURE 2 Hydrostatic pressures in renal cortical microvasculature.

From these direct estimates of P_{UF} and SNGFR, it was possible in the present study to obtain direct estimates of the ultrafiltration coefficient for these glomerular capillaries. Indirect estimates of K_f for rat glomerular capillaries, based on a number of assumed values, have been reported by Pappenheimer, Renkin, and Borrero (17) and yield values of approximately 250 $\times 10^{-8}$ ml/sec per cm H_2O/cm^2. Using data currently thought to be more representative of the normal rat, Renkin and Gilmore have revised this estimate (18) and obtain a slightly higher value of 400×10^{-8} ml/sec/cm H_2O/cm^2. By comparison, assuming the same estimate of glomerular capillary surface area (0.0019 cm^2 [19]) as used by Renkin and Gilmore (18), values for K_f in the present study (Table I) were uniformly higher than these previous indirect estimates, ranging from 960 to nearly 5200×10^{-8} ml/sec per cm H_2O/cm^2, and averaging 2300×10^{-8} ml/sec per cm H_2O/cm^2. In large part these higher values relative to previous estimates reflect the considerably lower P_{UF} measured in the present study. It should be pointed out that even these measured high estimates are likely to be minimum values in that we have assumed, as have these other

[4] Superficial cortical filtration fraction $= 1 - \frac{[\text{Protein}]_{FA}}{[\text{Protein}]_{EA}}$ where FA and EA refer to femoral artery and efferent arteriole, respectively.

[5] In recent studies from this laboratory (unpublished observations), $\bar{P}_{GC}$ was estimated indirectly in Sprague-Dawley rats after conditions of applied ureteral pressure as well as single tubule occlusion methods. Values for $\bar{P}_{GC}$, taken as the sum of P_T plus arterial plasma COP averaged 75 and 65 cm H_2O with each method. Similarly low estimates have also been reported recently by Hayslett, (15) and Andreucci (16) and their respective coworkers.

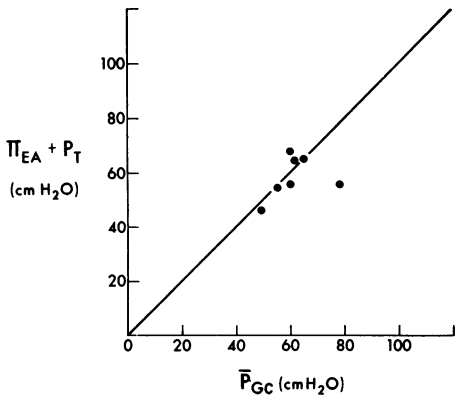

FIGURE 3 Comparison of values for $\bar{P}_{GC}$ and ($\pi_{EA} + P_T$). Filtration equilibrium is given by the line of identity. Symbols denote individual animals.

workers (17, 18), that COP rises as a linear function of glomerular capillary length. The more likely possibility, however, given the extreme leakiness of these glomerular capillaries to water, is that glomerular capillary plasma COP rises exponentially, approaching equilibrium conditions very near the beginning of the capillary segment. This is supported by the fact that even for extrarenal capillaries which have far lower K_f values that these glomerular capillaries 40×10^{-8} ml/sec per cm H_2O/cm^2 net fluid movement follows an exponential profile (20). Given these conditions the bulk of the glomerular ultrafiltrate would be formed across a relatively small fraction of the estimated available glomerular capillary surface area. Thus although the remaining fraction of the total capillary surface area would likely contribute little to ultrafiltrate formation, this additional length of capillary is still represented in the total surface area estimate used in the calculation of K_f. It is for this reason that we have preferred to express our values for K_f in the present study in the manner given in Table I.

It is not yet possible to estimate precisely where along the length of the glomerular capillary plasma COP reaches a value which, when added to P_T, closely approximates $\bar{P}_{GC}$ and thereby blunts further ultrafiltrate formation. That this equilibration does obtain however, is clearly demonstrated by the findings in the present study. Fig. 3 is an identity plot of the relationship between the measured value for $\bar{P}_{GC}$ and the sum of $\pi_{EA} + P_T$ for each of the seven rats studied. The finding of nearly identical values for these opposing pressures in six of seven rats (for all, $\pi_{EA} + P_T/\bar{P}_{GC} = 0.97$) provides evidence, in accord with earlier predictions (21), that filtration equilibrium normally obtains before entry of glomerular capillary blood into the efferent arteriole.

ACKNOWLEDGMENTS

We are grateful to Dr. Eugene M. Renkin and Dr. Joseph P. Gilmore for the opportunity to read unpublished material and to Dr. Curt A. Wiederhielm for rewarding discussions. Support for these studies was provided by the Veterans Administration (01/1073.1), National Institutes of Health (AM 13888) and American Hoechst Corp., Somerville, N. J.

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