Adaptation of Glomerular Forces and Flows to Renal Injury

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The mechanism of glomerular ultrafiltration in normal kidneys or after renal injury is reviewed. The role of increased glomerular plasma flow in mediating increases of nephron filtration rate is evidenced under experimental conditions resulting in filtration pressure disequilibrium along glomerular capillaries. The increase of nephron filtration in hypertrophied kidneys appears to be due mainly to a rise of glomerular plasma flow and, to a smaller extent, to an increase of glomerular capillary hydrostatic pressure, the ultrafiltration coefficient remaining unchanged. In contrast, in the early phases of experimentally induced nephrototoxic serum nephritis, a decrease of the ultrafiltration coefficient was observed; nephron filtration rate, however, remained within the normal range, as a consequence of a higher hydrostatic pressure in the glomerular capillaries of the nephritic kidneys.

INTRODUCTION

Despite significant advances in our understanding of the immunological and morphological aspects of a variety of disorders involving the kidney in which the glomerular filtration rate (GFR) of water is affected, there has been, until recently, relatively little information concerning the mechanisms responsible for these changes in GFR. This is due in large part to the fact that glomeruli are seldom encountered as surface structures in the mammalian kidney and are therefore inaccessible to direct study in vivo. This restriction has been overcome, however, with the availability of the so-called “Munich-Wistar” strain of rats which possess surface glomeruli. This advantage, together with technological and methodological developments allowing the direct assessment of hydraulic and oncotic pressures in the glomerular and periglomerular microcirculation [1,2] has made possible an analysis of the determinants of fluid and solute filtration in this mammalian species. This review will summarize our current understanding of the process of glomerular ultrafiltration, both in the normal state and in response to renal injury.

NORMAL GLOMERULAR DYNAMICS

The rate of production of a nearly ideal ultrafiltrate of plasma across the glomerular capillary walls, as in other capillary beds, is governed by the imbalance between the transcapillary hydraulic and colloid osmotic pressures. At any point along a glomerular capillary the local rate of ultrafiltration, \( J_u \), equals \( k (\Delta P - \Delta \Pi) \) where \( k \) is the effective hydraulic permeability of the capillary wall, and \( \Delta P \) and \( \Delta \Pi \) are the transcapillary hydraulic and colloid osmotic pressure differences, respectively. \( \Delta P \) is the difference between glomerular capillary hydraulic pressure, \( P_{GC} \), and Bowman's space hydraulic pressure, \( P_T \), while \( \Delta \Pi \) refers to the corresponding colloid osmotic pressure difference between the glomerular capillaries (\( \Pi_{GC} \)) and Bowman's space (\( \Pi_T \)). Under normal hydropenic conditions \( P_{GC} \) has been found to...
average approximately 45 mmHg in both the Munich-Wistar rat [3,4,5,6,7,8,9], and the squirrel monkey [10] while $P_T$ averages approximately 10 mmHg. $\Delta P$, the difference between these values of $P_{GC}$ and $P_T$ averaged along the length of the glomerular capillary, is therefore equal to approximately 35 mmHg. In the rat, $\Delta \Pi$ (equal to $\Pi_{GC}$ since $\Pi_T$ is negligible) [11], increases from a value of about 20 mmHg at the afferent end ($\Pi_A$) of the capillary network to approximately 35 mmHg at the efferent end ($\Pi_E$). The net local driving force for ultrafiltration $P_{UF}$, therefore declines from a maximum value of about 15 mmHg at the afferent end of the glomerulus to zero at the efferent end. Thus, by the efferent end of the capillary network, $\Delta \Pi$ rises to a value which, on the average, exactly equals $\Delta P$ [3,4,5,6,7,8,9,10]. This equality of $\Delta P$ and $\Delta \Pi$ is referred to as filtration pressure equilibrium.

SNGFR, the single nephron filtration rate for the glomerulus as a whole, is the product of the ultrafiltration coefficient, $K_f$, and the net driving pressure averaged over the length of the capillary network, $\overline{P}_{UF}$. $\overline{P}_{UF}$ is the difference between the mean transcapillary hydraulic and oncotic pressure differences, $\Delta P$ and $\Delta \Pi$, respectively. $K_f$ is the product of the effective hydraulic permeability of the capillary wall and the surface area available for filtration. When filtration pressure equilibrium exists it is not possible to estimate $\overline{P}_{UF}$, and hence, $K_f$, due to the uncertainty in determining the exact $\Delta \Pi$ profile.

A variety of studies designed to examine how variations in glomerular transcapillary pressures result in changes in SNGFR have revealed that such changes in SNGFR result primarily from variations in the rate of rise in $\Delta \Pi$, rather than from large changes in $\Delta P$ [4,5,7,9,12]. Alterations in the rate of rise of $\Delta \Pi$ result from variations in the rate of glomerular plasma flow ($Q_A$), with increases in $Q_A$ tending to displace the point at which filtration pressure equilibrium is reached further toward the efferent end of the glomerular capillary [13]. As a result, $\overline{P}_{UF}$ increases, leading to an increase in SNGFR. Decreases in $Q_A$ have the opposite effect. It has been concluded from these observations that SNGFR is highly plasma-flow dependent.

Since, under conditions of filtration pressure equilibrium, it is not possible to distinguish among the many $\Delta \Pi$ profiles consistent with equilibrium, only a minimum value of $K_f$ can be estimated. If, however, $Q_A$ is increased to levels above normal so that $\Delta \Pi$ no longer rises to a value large enough to equal $\Delta P$, a condition of filtration pressure disequilibrium will obtain. Under this condition a unique $\Delta \Pi$ profile can be computed from the measured values of afferent and efferent protein concentration, $\Delta P$ and $Q_A$ using the mathematical model of glomerular filtration derived by Deen, Robertson and Brenner [13].

This approach of increasing $Q_A$ to levels high enough to ensure disequilibrium in order to estimate the value of $K_f$ in the Munich-Wistar rat has been achieved both by intravenous infusion of isoncotic rat plasma [12] and by isovolemic reduction in hematocrit [7]. In both instances $K_f$ was found to average about 5 nl/(min . mmHg). Furthermore, $K_f$ remained essentially unchanged over a twofold range of changes in $Q_A$ [12], suggesting that $K_f$ does not vary with $Q_A$.

RESPONSE TO REDUCED RENAL MASS

Reduction in functional renal mass, when the result either of partial surgical ablation or a primary non-glomerular disease such as pyelonephritis, generally leads to an adaptive increase in the rate of glomerular filtration in surviving nephrons [5,14,15,16,17,18,19]. To ascertain the basis for this increase in GFR Deen et al. [5]
recently examined glomerular dynamics in uninephrectomized Munich-Wistar rats studied 2–4 weeks after surgery. During compensatory hypertrophy both total GFR and the total renal mass of the remaining kidney increased by approximately 50 percent: both SNGFR and \( Q_A \) increased proportionally to total GFR following uninephrectomy with single nephron filtration fraction (SNFF) remaining relatively constant. Despite the absence of significant differences in systemic arterial pressure (\( \Delta P \)) between the two groups, \( \Delta P \) was significantly higher after uninephrectomy, averaging about 40 mmHg, compared to 34 mmHg in controls. This was entirely the consequence of an increase in \( P_{GC} \), \( P_T \) remaining unchanged. There was no difference of \( \Pi_A \) between the two groups and filtration pressure equilibrium was observed in both groups of rats. Thus, the increase in SNGFR following uninephrectomy could have resulted from an increase in \( K_f \), \( P_{UF} \), or both. As discussed above, unique values for \( K_f \) cannot be determined under conditions of filtration pressure equilibrium. To estimate \( K_f \) for uninephrectomized rats, Deen et al. [5] produced disequilibrium by isoncotic plasma expansion, which had the desired effect of increasing \( Q_A \). Under these conditions \( K_f \) was found to average 4.7 nl/(min \cdot mmHg), a value similar to that found in non-nephrectomized control rats [7,12]. Since \( \Pi_A \) and \( K_f \) were essentially unchanged following uninephrectomy, the observed increase in the mean net ultrafiltration pressure, \( P_{UF} \), and increasing in SNGFR, must have been the consequence of the increases in \( Q_A \) and \( \Delta P \). The individual contribution of changes in \( Q_A \) and \( \Delta P \) to the observed changes in SNGFR was evaluated by calculation [13]: 70 percent of the compensatory increase in SNGFR was due to a rise in \( Q_A \), the remainder being due to an increase in \( \Delta P \).

In agreement with these findings, Kaufman et al. [18] observed that a 50 percent reduction in renal mass in the rat resulted in proportional increases in SNGFR and \( Q_A \), with SNFF remaining the same as in non-nephrectomized control rats. Following 75 percent ablation of renal mass, however, SNGFR and \( Q_A \) increased further, but now with a decrease in SNFF. Assuming that there was no substantial fall in \( \Delta P \) or increase in \( \Pi_A \) in the animals studied by Kaufman et al. [18], the further increase in \( Q_A \) to remaining nephrons probably produced filtration pressure disequilibrium. Thus, it appears that following 50 percent, or even 75 percent, reduction in renal mass, the compensatory increases in SNGFR are primarily governed by the extent to which \( Q_A \) increases in surviving nephrons. Here again, the results agree well with the earlier conclusion that GFR is highly plasma-flow dependent.

**RESPONSE TO PRIMARY GLOMERULAR INJURY**

In contrast to the observed increases in SNGFR which tend to minimize the degree of reduction in total GFR that would otherwise occur when renal mass is reduced by surgical ablation, progressive destruction of glomerular capillaries in a variety of glomerulopathic states is generally attended by reductions in both the whole kidney and single nephron GFR. Little is known about forces governing glomerular ultrafiltration in these glomerulopathies despite considerable advances in our understanding of the morphological and immunological aspects of these disorders.

Maddox et al. [6], however, have recently examined the forces determining glomerular filtration in Munich-Wistar rats 1 to 2 weeks following induction of a mild to moderate form of nephrotoxic serum nephritis (NSN). Light and electron microscopy both revealed that the proliferative inflammatory response associated with this form of glomerular injury caused partial or complete obliteration of some capillary loops, while other capillaries appeared essentially normal. Despite this morphologic evidence of widespread glomerular injury, glomerular filtration rates
(single nephron and whole kidney) and glomerular plasma flow rates ($Q_A$) were not different, on average, from values in non-nephritic control rats. In NSN, $\Delta P$ was elevated considerably above normal, due solely to increases in $P_{GC}$. Since $Q_A$ and $\Pi_A$ remained essentially constant, the failure of SNGFR to rise in response to the increase in $\Delta P$ in NSN rats was the consequence of a concomitant reduction in $K_f$, to a value averaging one-third of normal. Allison, Wilson and Gottschalk [19] have similarly observed reduction in $K_f$ in studies of more severe NSN as well as Heymann's nephritis in the rat. It is likely that the fall in $K_f$ observed in NSN rats is at least partly the result of the reduction in the number of patent capillaries in each glomerulus, i.e., a reduction in surface area available for ultrafiltration. Whether a decrease in effective hydraulic permeability ($k$) also contributes to the fall in $K_f$ cannot be ascertained from morphological considerations. Evidence for a decline in $k$ has been provided, however, by the recent findings of Blantz and Wilson [20], who observed a fall in $K_f$ one hour after intravenous injection of nephrotoxic serum. So early after injection of nephrotoxic serum, the number of patent glomerular capillaries was found not to be reduced appreciably, so that a fall in $k$, rather than a reduction in surface area, was postulated to account for the observed marked fall in $K_f$.

In the study of Maddox et al. [6] in the early stage of NSN, SNGFR and total kidney GFR remained at normal levels despite a fall in $K_f$ to one-third of normal, because of the compensating effect of an increase in $\Delta P$. If $\Delta P$ remains elevated in chronic glomerulonephritis, as suggested by the findings of Allison et al. [19], the progressive deterioration in filtration rate characteristically noted in more advanced stages of this disorder must result from further reductions in $K_f$ and/or declines in $Q_A$.

REFERENCES

1. Wiederhiem CA, Woodbury JW, Kirk S, Rushmer RF: Pulsatile pressures in the microcirculation of frog's mesentery. Am J Physiol 207:173–176, 1964
2. Brenner BM, Falchuk KH, Keimowitz RI, Berliner RW: The relationship between peritubular capillary protein concentration and fluid reabsorption by the renal proximal tubule. J Clin Invest 48:1519–1531, 1969
3. Brenner BM, Troy JL, Daugharty TM: The dynamics of glomerular ultrafiltration in the rat. J Clin Invest 50:1776–1780, 1971
4. Brenner BM, Troy JL, Daugharty TM, Deen WM, Robertson CR: Dynamics of glomerular ultrafiltration in the rat. II. Plasma-flow dependence of GFR. Am J Physiol 223:1184–1190, 1972
5. Deen WM, Maddox DA, Robertson CR, Brenner BM: Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass. Am J Physiol 277:556–562, 1974
6. Maddox DA, Bennett CM, Deen WM, Glasscock RJ, Knudsen D, Daugharty TM, Brenner BM: Determinants of glomerular filtration in experimental glomerulonephritis in the rat. J Clin Invest 55:305–318, 1975
7. Myers BD, Deen WM, Robertson CR, Brenner BM: Dynamics of glomerular ultrafiltration in the rat. VIII. Effects of hematocrit. Circ Res 36:425–435, 1975
8. Blantz RC: Effect of mannitol on glomerular ultrafiltration in the hypophenic rat. J Clin Invest 54:1135–1143, 1974
9. Chang RLS, Ueki IF, Troy JL, Deen WM, Robertson CR, Brenner BM: Permeselectivity of the glomerular capillary wall to macromolecules. II. Experimental studies in rats using neutral dextran. Biophys J 15:887–906, 1975
10. Maddox DA, Deen WM, Brenner BM: Dynamics of glomerular ultrafiltration. VI. Studies in the primate. Kidney Int 5:271–278, 1974
11. Eisenbach GM, Van Liew JB, Boylan JW: Effect of angiotensin on the filtration of protein in the rat kidney: A micropuncture study. Kidney Int 8:80–87, 1975
12. Deen WM, Troy JL, Robertson CR, Brenner BM: Dynamics of glomerular ultrafiltration in the rat. IV. Determination of the ultrafiltration coefficient. J Clin Invest 52:1500–1508, 1973
13. Deen WM, Robertson CR, Brenner BM: A model of glomerular ultrafiltration in the rat. Am J Physiol 223:1178–1183, 1972
14. Allison MEM, Lipharm EM, Lassiter WE, Gottschalk CW: The acutely reduced kidney. Kidney Int 3:354–363, 1973
15. Bank N, Aynedjian HS: Individual nephron function in experimental pyelonephritis. I. Glomerular filtration rate and proximal tubular sodium, potassium and water reabsorption. J Lab Clin Med 68:713–737, 1966
16. Gottschalk CW: Function of the chronically diseased kidney. The adaptive nephron. Circ Res 28 and 29, Suppl II:1–13, 1971
17. Hayslett JP, Kashgarian M, Epstein FH: Functional correlates of compensatory renal hypertrophy. J Clin Invest 47:774–782, 1968
18. Kaufman JM, Di Meola HJ, Siegel NJ, Lytton B, Kashgarian M, Hayslett JP: Compensatory adaptation of structure and function following progressive renal ablation. Kidney Int 6:10–17, 1974
19. Allison MEM, Wilson CB, Gottschalk CW: Pathophysiology of experimental glomerulonephritis in rats. J Clin Invest 53:1402–1423, 1974
20. Blantz RC, Wilson CB: Glomerular filtration following acute immunological injury. Am Soc Nephrol 8:60, 1975, Abstr