Effective glomerular filtration pressure and single nephron filtration rate during hydropenia, elevated ureteral pressure, and acute volume expansion with isotonic saline

Vittorio E. Andreucci, … , Floyd C. Rector Jr., Donald W. Seldin

Concise Publication

Free-flow and stop-flow intratubular pressures were measured in rats with an improved Gertz technique using Landis micropipets or a Kulite microtransducer. In hydropenia, average single nephron glomerular filtration rate was 29.3 nl/min, glomerular hydrostatic pressure (stop-flow pressure + plasma colloid osmotic pressure) was 70 cm H_2O and mean glomerular effective filtration pressure was 12.7-14.3 cm H_2O, approaching zero at the efferent end of the glomerulus. Thus, the glomerulus is extremely permeable, having a filtration coefficient four to five times greater than previously estimated. Mean effective filtration pressure and single nephron glomerular filtartion rate fell with elevated ureteral pressure and rose with volume expansion, more or less proportionately. Changes in effective filtration pressure were due primarily to increased intratubular pressure in ureteral obstruction and to reduced plasma colloid osmotic pressure in volume expansion; glomerular hydrostatic pressure remained constant in both conditions and thus played no role in regulation of filtration rate.

Find the latest version:

Effective Glomerular Filtration Pressure and Single Nephron Filtration Rate during Hydropenia, Elevated Ureteral Pressure, and Acute Volume Expansion with Isotonic Saline

Vittorio E. Andreucci, Jaime Herrera-Acosta, Floyd C. Rector, Jr., and Donald W. Seldin

From the Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Texas 75235

A B S T R A C T   Free-flow and stop-flow intratubular pressures were measured in rats with an improved Gertz technique using Landis micropipets or a Kulite microtransducer. In hydropenia, average single nephron glomerular filtration rate was 29.3 nl/min, glomerular hydrostatic pressure (stop-flow pressure + plasma colloid osmotic pressure) was 70 cm H_2O and mean glomerular effective filtration pressure was 12.7–14.3 cm H_2O, approaching zero at the efferent end of the glomerulus. Thus, the glomerulus is extremely permeable, having a filtration coefficient four to five times greater than previously estimated. Mean effective filtration pressure and single nephron glomerular filtartion rate fell with elevated ureteral pressure and rose with volume expansion, more or less proportionately. Changes in effective filtration pressure were due primarily to increased intratubular pressure in ureteral obstruction and to reduced plasma colloid osmotic pressure in volume expansion; glomerular hydrostatic pressure remained constant in both conditions and thus played no role in regulation of filtration rate.

INTRODUCTION

The driving force for glomerular filtration is the balance of hydrostatic and oncotic pressures acting across the glomerular membrane. The exact value of these forces is not known due to inaccessibility of the glomerulus. Gertz, Mangos, Braun, and Pagel (1) suggested that glomerular hydrostatic presure (P_G)[1] could be estimated from intratubular pressure in nephrons in which filtration was stopped by an oil block; P_G was assumed to be the sum of the stop-flow pressure (SFP) and arterial oncotic pressure. Gertz estimated net effective filtration pressure (EFP) as the difference between SFP and free-flow intratubular pressure (ITP). Unfortunately, SFP obtained with this method has ranged between 85.7 cm H_2O (1) and 35 cm H_2O (2). Moreover, the calculation of EFP by Gertz et al. (1, 3) is incorrect in that it does not account for the rise in glomerular oncotic pressure owing to continuous filtration during free flow (4).

In the present studies we found that an important artifact may arise during the measurement of SFP as a result of repeated injections of small amounts of saline into the blocked tubule through the pressure-measuring pipet. Consequently, we have refined the method to avoid this source of error. In addition, in calculating the EFP, we have taken into account the rise in protein concentration that occurs within the glomerulus as a result of filtration. Finally, the relation between the various glomerular Starling forces and single nephron glomerular filtration rate (SNGFR) was examined in rats during hy-

[1] *Abbreviations used in this paper:* EFP, effective filtration pressure; FF, filtration fraction; GFR, total kidney filtration rate; ITP, intratubular pressure; P_G, glomerular hydrostatic pressure; π_a, oncotic pressure in the afferent arteriole; π_e, oncotic pressure in the efferent arteriole; RBF, renal blood flow; SFP, stop-flow pressure; SNGFR, single nephron glomerular filtration rate.

dropenia, elevated ureteral pressure, and acute volume expansion with isotonic saline.

METHODS

Sprague-Dawley rats, anesthetized with Inactin (100 mg/kg), were prepared for micropuncture (5). In rats studied during elevated ureteral pressure (group I), a catheter in the left ureter was raised to 25 cm above the kidney. Bicarbonate-saline was infused at 0.02 ml/min during hydropenic control periods and during elevated ureteral pressure. Animals undergoing saline diuresis received bicarbonate-saline at the following rates:

Group II, mild volume expansion. 10% of body weight over a period of 45 min, then at a rate equal to urine flow (0.1–0.2 ml/min).

Group III, massive volume expansion. 0.4 ml/min throughout the experimental period. 60 min were allowed for equilibration before starting micropuncture collections or pressure measurements.

Total kidney filtration rate (GFR) and SNGFR were measured as previously described (5) using tritiated or ^{14}C-labeled inulin. Filtration fraction (FF) and renal blood flow (RBF) were calculated from renal extraction of inulin; blood was obtained from the left renal vein by puncture with heparinized micropipets. Plasma protein concentrations were measured by the Lowry technique.

Intratubular pressures during free-flow and stop-flow conditions were measured either by the Landis technique (6) using lissamine green-filled micropipets or with a Kulite microtransducer (7). SFP was measured in tubules blocked with castor oil (1). Initially, with the Landis technique, we observed that tubular fluid was forced into the lissamine green-filled pipet while the tubule was being filled with oil. When this tubular fluid was ejected back into the oil-blocked tubule in order for the dye to be visible at the pipet tip, SFP was artifactually elevated by several centimeters H_2O. This source of error could be avoided by maintaining slight positive pressure in the Landis pipet while filling the tubule with oil so that tubular fluid did not enter the pipet tip. When this precaution was observed, values of SFP obtained with the Landis technique were almost identical with those obtained with the Kulite microtransducer: 42.6 and 44.4 cm H_2O in two groups of hydropenic rats (Table I, groups I and II) with the Landis technique and 44.8 cm H_2O (Table I, group III) with the Kulite microtransducer. When SFP was measured by both methods in the same animal, the difference between the mean values obtained with each method was 0.8 cm H_2O (n = 12).

P_G was calculated as $P_G = SFP + \pi_a$; where π_a is the oncotic pressure in the afferent arteriole calculated from the arterial plasma protein concentration by the Landis-Pappenheimer equation (4). EFP at the afferent end of the glomerulus was calculated as Aff EFP = $P_G - \pi_a - $ ITP. EFP at the efferent end of the glomerulus was calculated as Eff EFP = $P_G - \pi_e - $ ITP, where π_e is the oncotic pressure in the efferent arteriole calculated from the plasma protein concentration in the efferent arteriole; the latter was obtained from the equation [Prot]$_{aff}$/1-FF (8). Glomerular EFP was calculated as EFP = $P_G - \pi_G - $ ITP, where π_G is the mean glomerular oncotic pressure $(\pi_a - \pi_e)/2$.

RESULTS

Results are summarized in Table I.

Hydropenia. There was close agreement in the three hydropenic control groups. The slight differences observed might be related to the fact that rats in groups I and II weighed 180–222 g, while those in group III weighed 250–300 g. In all groups, ITP was approximately 20 cm H_2O and P_G was approximately 70 cm H_2O. EFP at the afferent end of the glomerulus was approximately 25 cm H_2O and at the efferent end of the glomerulus was very close to zero, ranging from 1.6 to 2.9 cm H_2O. Mean glomerular EFP ranged from 12.7 to 14.3 cm H_2O. SNGFR ranged from 27.0 to 32.5 nl/min (mean = 29.3 ±0.8; n = 132).

Elevated ureteral pressure (group I, 13 rats). When ureteral pressure was raised to 25 cm H_2O, GFR fell from 1.49 ml/min to 0.83 ml/min and RBF rose 8%. ITP increased to 29.2 cm H_2O but SFP did not change. Since π_a also was relatively constant, calculated P_G was unchanged. Because of the rise in ITP, the EFP at the afferent end of the glomerulus fell to 15.4 cm H_2O. EFP at the efferent end of the glomerulus was again close to zero (3.5 cm H_2O). Mean glomerular EFP fell to 9.4 and SNGFR was reduced to 12.7 nl/min. Peritubular capillary hydrostatic pressure rose from a control of 16 cm H_2O to 22 cm H_2O.

Mild volume expansion (group II, 12 rats). During mild volume expansion, GFR and RBF increased 25 and 20% respectively, while Na excretion rose from 0.09 μEq/min to 3.83 μEq/min. A slight, but significant increase was observed in both ITP and SFP. Plasma protein concentration and π_a decreased markedly. Calculated P_G fell slightly to 62.7 cm H_2O. Afferent EFP was unchanged. As a result of a fall in plasma protein concentration and FF, efferent EFP was no longer close to zero, but instead rose to 17.5 cm H_2O. Mean glomerular EFP rose to 22.1 cm H_2O and SNGFR rose to 34.5 nl/min. Peritubular capillary hydrostatic pressure rose 3 cm H_2O.

Massive volume expansion (group III, 21 rats). During massive volume expansion GFR rose 19%, RBF increased 15%, and sodium excretion increased from 0.09 μEq/min to 16.7 μEq/min. ITP increased to 28.1 cm H_2O, while SFP rose to 57.7 cm H_2O. EFP rose to 29.6 cm H_2O at the afferent end of the glomerulus and to 23.1 cm H_2O at the efferent end. Mean EFP rose to 26.3 cm H_2O while SNGFR rose to 46.0 nl/min. Peritubular capillary hydrostatic pressure rose from 16 to 21 cm H_2O.

DISCUSSION

It has been assumed, on the basis of indirect evidence, that glomerular hydrostatic pressure is 70–80 mm Hg (9–11). The studies of Gertz et al. (1, 3), Krause, Dume, Koch, and Ochwadt (12) and Koch et al. (13) appeared to confirm such values, whereas several other investigators using the same technique obtained much lower values (2, 14–17). Our experience with the Gertz

TABLE I

Effect of Elevated Ureteral Pressure and Acute Volume Expansion on Glomerular Filtration Pressures and Single Nephron Filtration Rate

	Group I*		Group II*		Group III*	
	Hydropenia	Elevated ureteral pressure	Hydropenia	Mild volume expansion	Hydropenia	Massive volume expansion
ITP, cm H_2O	18.1 ±0.5 (n = 21)	29.2 ±0.9 (n = 20)	17.4 ±0.6 (n = 8)	22.2 ±0.8 (n = 15)	22.3 ±0.4 (n = 16)	28.1 ±0.9 (n = 15)
SFP, cm H_2O	42.6 ±1.2 (n = 21)	44.6 ±1.4 (n = 20)	44.4 ±1.0 (n = 8)	49.0 ±1.2 (n = 15)	44.8 ±1.3 (n = 16)	57.7 ±1.7 (n = 15)
Plasma protein, g/100 ml	5.84 ±0.17 (n = 16)	5.52 ±0.12 (n = 21)	5.50 ±0.29 (n = 11)	3.60 ±0.11 (n = 11)	5.84 ±0.10 (n = 16)	3.50 ±0.16 (n = 16)
π_a, cm H_2O	26.5	24.5	24.3	13.7	26.5	13.2
FF	0.33 ±0.03 (n = 7)	0.23 ±0.04 (n = 7)	0.37 ±0.01 (n = 7)	0.32 ±0.03 (n = 7)	0.30 ±0.02 (n = 9)	0.26 ±0.02 (n = 9)
π_e, cm H_2O	49.5	36.2	49.7	23.0	46.1	19.7
π_G, cm H_2O	38.0	30.4	37.0	18.4	36.3	16.5
P_G, cm H_2O	69.1	69.0	68.7	62.7	71.3	70.9
Afferent EFP, cm H_2O	24.5	15.4	27.0	26.8	22.5	29.6
Glomerular EFP, cm H_2O	13.2	9.4	14.3	22.1	12.7	26.3
Efferent EFP, cm H_2O	1.7	3.5	1.6	17.5	2.9	23.1
SNGFR nl/min	27.2 ±1.6 (n = 37)	12.7 ±1.0 (n = 33)	27.0 ±1.7 (n = 28)	34.5 ±2.3 (n = 30)	32.5 ±1.3 (n = 67)	46.0 ±1.5 (n = 76)
BP, mm Hg	127 ±9.9 (n = 10)	124 ±9.3 (n = 10)	131 ±17	129 ±2 (n = 7)	116 ±4 (n = 14)	115 ±4 (n = 14)

* Mean ±SE

ITP, free flow intratubular pressure; SFP, stop flow intratubular pressure; FF, filtration fraction; SNGFR, single nephron glomerular filtration rate; π_a, afferent glomerular oncotic pressure calculated from arterial plasma protein concentration (P_a) by the Landis and Pappenheimer equation (4):

$\pi_a = 2.1 P_a + 0.16 P_a^2 + 0.009 P_a^3$;

π_e, efferent glomerular oncotic pressure calculated from plasma protein concentration in the efferent arteriole (P_e) according to the Landis and Pappenheimer equation (4). P_e is calculated from $P_a/1-FF$ (8).

π_G, glomerular oncotic pressure calculated as $\pi_a + \pi_e/2$; P_G, glomerular hydrostatic pressure = SFP + π_a; afferent EFP = effective filtration pressure at the beginning of the glomerulus = $P_G-\pi_a$-ITP; glomerular EFP = mean effective filtration pressure = $P_G-\pi_G$-ITP; efferent EFP = effective filtration pressure at the efferent end of the glomerulus = $P_G-\pi_e$-ITP.

$$y = 0.70 + 1.68 x$$
$$r = 0.94$$

SNGFR nl/min

60
50
40
30
20
10
0

‡ Massive Volume Expansion

‡ Mild Volume Expansion

‡ Hydropenia

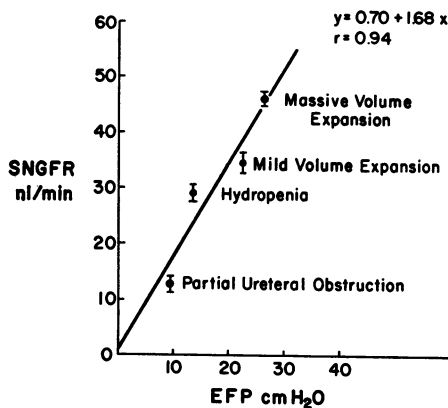‡ Partial Ureteral Obstruction

10 20 30 40

EFP cm H₂O

FIGURE 1 Relationship between glomerular effective filtration pressure (EFP) and single nephron filtration rate (SNGFR) in the rat kidney. The values of SNGFR are mean ±SE.

technique for measuring SFP suggests that a major cause of discrepant results is the variable amount of fluid injected into the oil-blocked tubule through the pressure-measuring pipet. When this error is avoided, we obtained SFP and calculated P_G of 45 and 70 cm H_2O, respectively. These values are lower than the values obtained by Gertz et al. (1, 3), but similar to those obtained by other investigators (2, 14–17).[2] The P_G in the range of 70 cm H_2O (50 mm Hg) in rats with BP of 110–130 mm Hg (within the autoregulation range) indicates that the pressure drop across the afferent arteriole is greater than across the efferent arteriole, i.e., resistance to blood flow is greater in the afferent than in the efferent arteriole.

As a consequence of the lower P_G than previously suspected, the mean EFP is also lower, ranging from 12.7 to 14.3 cm H_2O. One of the most unexpected features of the present studies was the finding that EFP was nearly zero at the efferent end of the glomerulus, indicating that glomerular filtration was approaching an equilibrium state. These findings indicate that the glomerulus is extremely permeable, having a filtration coefficient four to five times greater than that previously estimated.

Gertz et al. (3) suggested that the glomerular filtration coefficient was not constant, but instead changed in different physiologic conditions. They found that during saline diuresis, the rise in SNGFR was greater than the calculated rise in EFP, suggesting a significant increase in glomerular permeability. In our studies, how-

[2] Recent studies by Blantz et al. in our laboratory using mutant Wistar rats (generously supplied by Dr. K. Thurau and Dr. J. Boylan) and a servo-null micropressure transducer have shown that P_G measured by direct puncture of six glomeruli averaged 70 cm H_2O, agreeing with the values obtained indirectly by SFP measurements. P_G in these rats did not change in saline diuresis.

ever, changes in SNGFR and EFP are approximately proportional (Fig. 1). Both EFP and SNGFR fell with elevation of ureteral pressure and rose with volume expansion. The mean regression line through these points had a slope of 1.68 nl/min per cm H_2O and an intercept near the origin ($r = 0.94$). These observations suggest that there is no significant change in glomerular permeability in partial ureteral obstruction or saline diuresis.

Since both ureteral obstruction and volume expansion are known to induce renal vasodilatation, it is interesting to compare the manner in which EFP changed in these two conditions. Despite 8% increase in RBF in ureteral obstruction and 15–20% during saline diuresis, P_G remained constant (Table I). This indicates that, to the extent that renal vasodilatation occurred, both afferent and efferent arterioles dilated proportionately. The mechanism responsible for this precise interplay between afferent and efferent arteriolar resistances is not clear. Most theories concerned with autoregulation and control of renal vascular tone have focused primarily on the afferent arteriole and to a lesser extent on the efferent arteriole. The finding of constant P_G, however, suggests that both afferent and efferent arterioles respond in parallel to changes in neural tone, interstitial pressure, local concentrations of angiotensin II, or other unidentified factors. (It is unlikely that the renin-angiotensin system is involved in the maintenance of constant P_G in the present studies since renin release is enhanced in ureteral constriction and suppressed in saline diuresis.) An alternative possibility is that afferent arteriolar tone is the primary target of control by one or more factors, and that efferent arteriolar resistance responds secondarily, possibly by a passive myogenic mechanism, in a manner to maintain P_G constant. Not only do these changes in efferent tone serve to maintain constant P_G, but they also serve to regulate the transmission of hydrostatic forces to the peritubular capillary bed (capillary pressure in all of the present experiments despite constant P_G) and thus possibly to exert indirect control over tubular reabsorption.

In ureteral obstruction the fall in mean glomerular EFP was due primarily to the rise in ITP, although the effect of this rise in ITP was somewhat blunted by the fall in FF and consequent reduction in mean glomerular oncotic pressure. Despite increased blood flow, filtration still tended to approach equilibrium; efferent EFP was only 3.5 cm H_2O.

In both mild and massive saline diuresis, the rise in mean glomerular EFP was entirely attributable to the dilution of plasma proteins, the fall in FF contributed only a minor effect[3] and P_G remained constant. In con-

[3] One possible error might arise from the calculation of efferent EFP on the basis of whole kidney FF. The calculations are probably valid in hydropenia since Brenner and

trast to both hydropenia and partial ureteral obstruction, filtration did not approach equilibrium at the efferent end of the glomerulus; efferent EFP was 17.5 cm H_2O in mild volume expansion and 23.1 cm H_2O in massive volume expansion. Although the RBF was significantly higher during volume expansion, failure of filtration to reach equilibrium was probably not related to faster transit through the glomerulus, but more likely to the fact that oncotic pressure is an exponential function of plasma protein concentation (4). For this reason a FF of 0.3 would produce much less rise in glomerular oncotic pressure when entering protein concentration is 3.5 g/100 ml than when it is 5.8 g/100 ml.

The fact that filtration approaches equilibrium at the efferent end of the glomerulus in hydropenia but not in saline diuresis has important implications concerning the possible mediation of glomerulotubular balance by postglomerular oncotic forces (19, 20). Because of the relatively high plasma protein concentration during hydropenia, changes in GFR induced by altering renal perfusion pressure will result in marked changes in the oncotic pressure of blood issuing from the glomerulus into peritubular capillaries, whereas similar changes in GFR during saline diuresis and a lower plasma protein concentration will produce only minor changes in postglomerular oncotic pressure. This might serve to explain why proximal glomerulotubular balance is precisely maintained in hydropenia and only partially maintained during saline diuresis (21).

Galla (18) found that superficial nephron FF and whole kidney FF are very close. In saline diuresis, however, whole kidney FF may fall while FF in superficial nephrons does not change. If we recalculate mean glomerular EFP in groups II and III on the basis of hydropenic FF, mean glomerular EFP would be 20.8 instead of 22.1 cm H_2O in group II and 25.6 instead of 26.3 cm H_2O in group III. Thus, in saline diuresis when plasma protein concentration is low, the actual FF used in the calculation has little effect on estimated EFP.

REFERENCES

1. Gertz, K. H., J. A. Mangos, G. Braun, and H. D. Pagel. 1966. Pressure in the glomerular capillaries of the rat kidney and its relation to arterial blood pressure. *Pflüegers Arch.* **288:** 369.
2. Rocha, A., M. Marcondes, and G. Malnic. 1971. Micropuncture study of individual nephrons in rats with experimental nephrotic syndrome. *J. Clin. Invest.* In press.
3. Gertz, K. H., M. Brandis, G. Braun-Schubert, and J. W. Boylan. 1969. The effect of saline infusion and hemorrhage on glomerular filtration pressure and single nephron filtration rate. *Pflüegers Arch.* **310:** 193.
4. Landis, E. M., and J. R. Pappenheimer. 1963. Exchange of substances through the capillary walls. *Handb. Physiol. Sect. 2. Circulation.* **2:** 961.
5. Andreucci, V. E., J. Herrera-Acosta, F. C. Rector, Jr., and D. W. Seldin. 1971. Measurement of single nephron glomerular filtration rate by micropuncture. Analysis of error. *Amer. J. Physiol.* In press.
6. Landis, E. M. 1926. The capillary pressure in frog mesentery as determined by micropuncture methods. *Amer. J. Physiol.* **75:** 548.
7. Wunderlich, P., and J. Schnermann. 1969. Continuous recording of hydrostatic pressure in renal tubules and blood capillaries by use of a new pressure transducer. *Pflüegers Arch.* **313:** 89.
8. Bresler, E. H. 1956. The problem of the volume component of body fluid homeostasis. *Amer. J. Med. Sci.* **232:** 93.
9. Winton, F. R. 1951-52. Hydrostatic pressures affecting the flow of the urine and blood in the kidney. *Harvey Lect.* 67.
10. Pappenheimer, J. R. 1955. Über die Permeabilität Glomerulummembranen in der Niere. *Klin. Wochenschr.* **33:** 362.
11. Thurau, K. 1964. Renal hemodynamics. *Amer. J. Med.* **36:** 698.
12. Krause, H. H., T. Dume, K. M. Koch, and B. Ochwadt. 1967. Intratubulärer Druck, glomerulärer Capillardruck und Glomerulumfiltrat nach Furosemid und Hydrochlorothiazid. *Pflüegers Arch.* **295:** 80.
13. Koch, K. M., T. Dume, H. H. Krause, and B. Ochwadt. 1967. Intratubulärer Druck, glomerulärer Capillardruck und Glomerulumfiltrat Während Mannit-Diurese. *Pflüegers Arch.* **295:** 72.
14. Henry, L. N., C. E. Lane, and M. Kashgarian. 1968. Micropuncture studies of the pathophysiology of acute renal failure in the rat. *Lab. Invest.* **19:** 309.
15. Wikstrom, D. I., and M. A. Cortney. 1968. Glomerular filtration rate and proximal tubular reabsorption as affected by volume expansion in the rat. 2nd Annual Meeting American Society Nephrology, Washington 70. (Abstr.)
16. Jaenike, J. R. 1969. Micropuncture study of methemoglobin-induced acute renal failure in the rat. *J. Lab. Clin. Med.* **73:** 459.
17. Hayslett, J. P., D. T. Domoto, M. Kashgarian, and F. H. Epstein. 1970. Role of physical factors in the natriuresis induced by acetylcoline. *Amer. J. Physiol.* **218:** 880.
18. Brenner, B. M., and J. H. Galla. 1971. Influence of postglomerular hematocrit and protein concentration on rat nephron fluid transfer. *Amer. J. Physiol.* **220:** 148.
19. Lewy, J. E., and E. E. Windhager. 1968. Peritubular control of proximal tubular fluid reabsorption in the rat kidney. *Amer. J. Physiol.* **214:** 943.
20. Brenner, B. M., and J. L. Troy. 1971. Postglomerular vascular protein concentration: evidence for a causal role in governing fluid reabsorption and glomerulotubular balance by the renal proximal tubule. *J. Clin. Invest.* **50:** 336.
21. Rodicio, J., J. Herrera-Acosta, J. C. Sellman, F. C. Rector, Jr., and D. W. Seldin. 1969. Studies on glomerulotubular balance during aortic constriction, ureteral obstruction and venous occlusion in hydropenic and saline-loaded rats. *Nephron.* **6:** 437.