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### Concise Publication

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# Nephron Stop-Flow Pressure Response to Obstruction for 24 Hours in the Rat Kidney

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**ABSTRACT** Complete ureteral ligation of 24-h duration significantly reduced stop-flow and estimated glomerular capillary pressures in nephrons accessible to micropuncture in obstructed kidneys. In kidneys without ureteral obstruction, a similar response occurred in single tubules blocked for 24 h without affecting nearby unblocked tubules. Thus, the response to tubular obstruction occurs on an individual nephron basis and results from constriction of individual afferent arterioles. The mechanism leading to the response is unknown, but a feedback mechanism operating through the juxtaglomerular apparatus of individual nephrons is an attractive possibility.

## INTRODUCTION

In a recent study of the pathophysiological mechanisms responsible for the development of oliguric acute renal insufficiency after 1 h of unilateral renal arterial occlusion in the rat, we found that immediately after restoration of blood flow, proximal intratubular hydrostatic pressures (PITP)<sup>1</sup> were markedly elevated above normal, while stop-flow (SFP) and estimated glomerular capillary pressures (GCP) were unchanged (1). These observations indicated that tubular obstruction was an initial event in the genesis of oliguria. Examination of histological sections supported this conclusion. 24 h after the ischemic period, however, SFP and renal blood flow were significantly reduced, although PITP and systemic arterial pressure were normal, which suggests a sec-

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<sup>1</sup>Abbreviations used in this paper: AP, arterial pressures; GCP, glomerular capillary pressures; JGA, juxtaglomerular apparatus; PITP, proximal intratubular hydrostatic pressures; SFP, stop-flow pressures.

ondary development of augmented preglomerular vascular resistance.

In order to further evaluate the relationship between tubular obstruction and SFP, and to determine whether a similar delayed reduction in SFP would follow other means of interruption of tubular fluid flow without the complicating features associated with a period of renal ischemia and hypoxia, we measured PITP and SFP in two groups of animals. In one group, a ureter was ligated, and in the other, individual nephrons were obstructed. We found that obstruction of 24-h duration in whole kidneys and in individual nephrons significantly reduced SFP.

## METHODS

Observations are reported on a total of 12 male Wistar rats, weighing 210–340 g, which were deprived of food overnight but allowed free access to water. The rats were anesthetized by intraperitoneal injection of sodium pentobarbital, 50 mg/kg body wt, placed on a heated table, and the left kidney was exposed through an abdominal incision for micropuncture, as previously described (2). An intravenous infusion of 0.85% NaCl at a rate of 40  $\mu$ l/min was given to replace fluid losses. Afferent GCP was estimated from the sum of plasma oncotic and SFP. To measure SFP, fresh oil was introduced in a retrograde manner into previously obstructed and into unobstructed proximal tubules until the earliest accessible proximal loop was identified; the hydrostatic pressure was measured by using an electronic servo-nulling device. Protein concentration in systemic plasma was determined by an adaptation of the Lowry technique (3), and oncotic pressure was calculated by the Landis and Pappenheimer equation (4). Blantz, Isrealit, Rector, and Seldin (5) have shown that GCP were similar in nondiuretic mutant Wistar rats, whether measured directly in superficial glomeruli or estimated from the sum of stop-flow hydrostatic and systemic plasma oncotic pressures. Arterial pressure (AP) was measured in a femoral artery with a Statham pressure transducer (Statham Instruments, Inc., Oxnard, Calif.) connected to a Beckman Dynograph (Beckman Instruments, Inc., Fullerton, Calif.).

TABLE I  
Influence of Unilateral Ureteral Ligation for 24 h  
on PITP and SFP

	Control*	Ureteral ligation	P
SFP, mm Hg	38.4±1.9	22.6±3.3	<0.001
PITP, mm Hg	12.6±2.3	12.0±1.2	NS
SFP-PITP, mm Hg	26.2±3.1	10.5±3.8	<0.001
AP, mm Hg	105±12	114±11	NS
Number of animals	7	7	
Number of observations	15	40	

Values are mean ±1 SD, calculated from the mean per animal. AP, Femoral arterial pressure.

Calculated oncotic pressure was 15.6±1.8 mm Hg (*n* = 5) during control conditions and 13.7±2.0 mm Hg (*n* = 5) in the ureteral ligation group. Thus estimated, GCP averaged 54 and 37 mm Hg (*P* < 0.001) for control and ureteral ligation animals.

\* Data obtained from another series of nondiuretic rats (1).

In seven rats the left ureter was ligated through a suprapubic incision, and 24 h later the obstructed kidney was studied by micropuncture. In five other rats the left kidney was exposed through a small flank incision and was immobilized by placing a lucite ring and cotton around it. Using sharpened pipettes, approximately eight proximal tubules in each kidney were almost completely filled with a column of Sudan black-stained castor oil. Only rarely were surface leaks of tubular fluid or oil visualized; these nephrons were not studied. The incision was closed, and 24 h later the kidney was prepared for micropuncture.

## RESULTS

After 24 h of continued ureteral occlusion, there were consistent reductions in SFP and estimated GCP in the presence of normal PITP and systemic AP. Effective filtration pressure (SFP - PITP) at the afferent end of glomerular capillaries was also lower, due to the decrease in SFP. The few intratubular and stop-flow pressures (nine observations, three animals) that were measured immediately after removal of the 24-h obstruction were essentially unchanged when compared to the values obtained during the observation period before removal. The pooled data are compared to values measured in control animals in Table I. In obstructed nephrons, one regularly observes PITP to be lower than SFP, as reabsorption of tubular fluid continues to the extent of available tubule proximal to the oil block. For this reason it is imperative that SFP be determined in the earliest proximal loop rather than at random sites along the tubule.

To determine if such a response could be produced in single nephrons, individual tubules were obstructed with oil in another group of animals. 24 h later the obstructed surface convolutions were easily identifiable as variable

amounts of oil remained. In most instances, the blocked proximal convolutions were slightly dilated and had hydrostatic pressures that were higher than those in nearby unblocked tubules. SFP, estimated GCP, and afferent effective filtration pressure in each previously obstructed nephron studied in all five kidneys were appreciably lower than corresponding values in unobstructed tubules (Table II).

## DISCUSSION

Blockage of tubular flow for 24 h in individual nephrons elicited preglomerular vasoconstriction and decreased SFP in those nephrons to a degree remarkably similar to that seen 24 h after either unilateral ureteral obstruction or temporary unilateral renal arterial occlusion (1) when all or most of the nephron population was affected. 24 h after unilateral ureteral occlusion, Jaenike (6) found similar results. Complete unilateral ureteral occlusion for 24 h causes a reduction in renal blood flow (7). The delayed decreases in PITP and SFP contrast with the early effects of unilateral renal ischemia (1) and ureteral obstruction (6, 8) when SFP is normal or higher than normal.

Although a decrease in SFP always occurred after 24 h of ipsilateral ureteral or renal arterial occlusion, it was not apparent whether the changes in preglomerular vascular resistance were due to a recruitment effect, resulting from obstruction of the many thousands of nephrons in each kidney, or whether a similar delayed relationship between impaired tubular fluid flow and de-

TABLE II  
Influence of Oil Blockade to Tubular Flow in Individual  
Nephrons for 24 h on PITP and SFP

Animal	No. observed	SFP	PITP	SFP-PITP	AP
		mm Hg	mm Hg	mm Hg	mm Hg
Blocked nephrons					
A	4	21.0±3.7	15.4±2.3	5.6±2.9	118±7
B	6	30.7±3.9	15.2±4.4	15.5±5.0	118±1
C	4	22.6±4.4	14.4±2.9	8.1±6.5	98±1
D	6	27.8±3.6	17.2±5.5	10.6±4.8	128±2
E	4	28.0±1.6	16.4±5.0	11.6±4.6	131±4
Mean	5	26.0±4.1	15.7±1.1	10.3±3.7	119±13
Unblocked nephrons					
A	4	37.4±1.8	13.0±2.3	24.4±3.6	118±8
B	3	37.3±1.3	11.9±2.7	25.4±3.5	116±4
C	4	38.5±3.7	10.4±0.8	28.1±2.9	98±1
D	5	38.1±2.4	11.1±1.9	26.8±2.6	129±1
E	4	38.9±2.5	13.0±1.7	25.9±4.0	128±7
Mean	5	38.0±0.7	11.9±1.2	26.1±1.4	118±12
P		<0.001	<0.001	<0.001	NS

Values are mean ±1 SD. In the blocked and unblocked nephrons, estimated GCP averaged 39 and 51 mm Hg (*P* < 0.001), respectively, as calculated systemic plasma oncotic pressure was 13.1±2.9 mm Hg (*n* = 5).

creased SFP could occur strictly on an individual nephron basis, due to the involvement of a single afferent arteriole. The data presented in Table II clearly indicate that the relationship between prolonged tubular obstruction and SFP occurs on an individual nephron basis. The sequence of events and mechanism(s) by which prolonged tubular obstruction and restricted tubular fluid flow influence SFP and resistance of individual afferent arterioles of blocked tubules is not known. Although many explanations of our results are possible, including for example, a direct vascular response of the glomerulus to increased pressure in Bowman's space, involvement of a feedback control mechanism seems an attractive possibility.

Numerous investigators have suggested various types of tubulo-glomerular feedback mechanisms involving the juxtaglomerular apparatus (JGA). Response in glomerular and/or tubular function has been thought to result from a change in tubular fluid composition, flow, or pressure at the macula densa, which results in a change in renin and angiotensin activities in systemic blood. Thurau and Schnermann (9) were the first to present experimental evidence suggesting that a response presumably involving the JGA occurred on an individual nephron basis and resulted from angiotensin formation locally in the immediate vicinity of the afferent arteriole. Subsequently, Gottschalk and Leyssac (2) criticized Thurau and Schnermann's technique and suggested that their results were artifactual. In more recent studies Schnermann, Davis, Wunderlich, Levine, and Horster (10) and Schnermann, Persson, and Ågerup (11) have reported other evidence of a rapidly acting tubulo-glomerular feedback system altering filtration rate and estimated GCP on an individual nephron basis. In contrast, others have not been able to substantiate the operation of such a rapid acting control system in acute experiments (5, 12, 13).

Unequivocal evidence of control of nephron function on an individual nephron basis has been obtained in three recent studies of rats with various types of experimentally induced renal insufficiency (14-16). In each study, great heterogeneity of single nephron filtration rate was present in the remaining functional nephrons, yet proximal fractional reabsorption was the same in all tubules in individual kidneys. Thus, in some fashion, the rate of proximal reabsorption was adjusted on an individual nephron basis so that glomerulo-tubular balance was maintained at the same level in each nephron. Although the control mechanism(s) responsible for these results remains obscure, it could also involve a

feedback mechanism operating through individual JGA's. Alternative explanations include the possibility of glomerulo-tubular balance being determined by the relationship between peritubular and glomerular capillary blood flow existing on an individual nephron basis or by some more direct factor causing proximal tubular reabsorption to be dependent on intraluminal load. In such studies of glomerulo-tubular coupling, it is not clear which parameter undergoes the primary change and which is secondarily affected. In the studies we report here, obstruction of tubular flow results in some unknown fashion in a change in glomerular function in the same nephron.

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