Kidney International, Vol. 26 (1984), pp. 294–302

Tubuloglomerular feedback and interstitial pressure in obstructive nephropathy

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Tubuloglomerular feedback and interstitial pressure in obstructive nephropathy. The possible role of the tubuloglomerular feedback (TGF) mechanism in the altered glomerular hemodynamics and tubular reabsorption which occur with prolonged (24-hr) ureteral obstruction and the changes in renal interstitial hydrostatic and oncotic pressure which may modulate TGF sensitivity were examined. The proximal tubule stop-flow pressure (P_{SF}) response to increased distal tubular flow rates (TGF activity) was determined in rats with sham operation, 24-hr unilateral ureteral obstruction (UUO), or 24-hr bilateral ureteral obstruction (BUO), both before and for 2 hr after relief of obstruction. Subcapsular hydrostatic pressure, lymph flow and oncotic pressure, clearance and excretory data were measured in the second series of animals. During and after release of UUO, TGF sensitivity was increased, as indicated by the marked decrease in the loop perfusion rate at which 50% of the maximum decrease in P_{SF} occurred (the *turning point* of TGF activation). Interstitial oncotic pressure but not hydrostatic pressure was significantly increased in UUO kidneys. In BUO rats, the turning point for TGF activation was slightly higher than the controls and the change in P_{SF} with maximum loop perfusion rates was reduced, indicating a blunting of the TGF response before and particularly during postobstructive diuresis after release of BUO. Interstitial hydrostatic and oncotic pressures were both slightly increased resulting in no changes in net interstitial Starling forces. We conclude that enhanced TGF sensitivity after release of prolonged UUO, associated with increased interstitial oncotic pressure, may play a role in preventing postobstructive diuresis, while the blunting of TGF sensitivity after BUO may contribute to this phenomenon.

Rétrocontrôle glomérulo-tubulaire et pression interstitielle au cours de la néphropathie obstructive. Le rôle possible du mécanisme de rétrocontrôle glomérulo-tubulaire (TGF) dans l'altération de l'hémadynamique glomérulaire et la réabsorption tubulaire qui se produisent lors d'une obstruction urétérale prolongée (24 heures) et les modifications des pressions hydrostatiques et oncotiques interstitielles rénales qui pourraient moduler la sensibilité TGF ont été étudiés. La réponse de pression en flux interrompu (P_{SF}) du tubule proximal à une augmentation des débits tubulaires distaux a été déterminée chez des rats ayant subi un simulacre d'intervention, lors d'une obstruction urétérale unilatérale de 24 heures (UUO) ou lors d'une obstruction urétérale bilatérale de 24 heures (BUO), avant et 2 heures après la levée de l'obstruction. La pression hydrostatique sous-capsulaire, le flux et la pression oncotique lymphatiques, les paramètres de clearance et d'excrétion ont été mesurés chez une deuxième série d'animaux. Pendant et après levée de l'UUO, la sensibilité TGF a augmenté, comme le montrait la diminution marquée du débit de perfusion de l'anse pour lequel 50% de la chute maximale de P_{SF} se produisait (*le point d'inflexion* de l'activation TGF). La pression oncotique mais non la pression hydrostatique interstitielle était significativement accrue dans les reins UUO. Chez les rats BUO, le point d'inflexion de l'activation TGF était légèrement plus élevé que chez les contrôles, et la modification de P_{SF} aux débits de perfusion de l'anse maxima était diminuée, indiquant une altération de la réponse TGF avant et surtout pendant la diurèse post-obstructive, après levée de la BUO. Les pressions interstitielles hydrostatiques et oncotiques légèrement augmentées, d'où l'absence de modification des forces de Starling interstitielles nettes. Nous concluons que l'augmentation de la sensibilité TGF après levée d'une UUO prolongée associée à une élévation de la pression oncotique interstitielle, pourrait jouer un rôle pour prévenir la diurèse postobstructive, alors que l'altération de la sensibilité TGF après BUO pourrait contribuer à ce phénomène.

Although the pathophysiology of experimental obstructive nephropathy has been extensively studied in recent years, many questions remain [1]. The possible role of the tubuloglomerular feedback mechanism in the altered glomerular hemodynamics and tubular reabsorption which occur with prolonged (24-hr) ureteral obstruction has not been determined. Recent evidence [2, 3] indicates that interstitial pressure may modulate the sensitivity of tubuloglomerular feedback (TGF) to changes in distal tubular flow rate such that increased interstitial hydrostatic pressure or decreased oncotic pressure, for example, during volume expansion, will reduce TGF sensitivity, while decreased interstitial hydrostatic pressure and increased oncotic pressure, for example, during dehydration, will enhance TGF sensitivity. The aim of the present experiments was to compare the sensitivity of the TGF mechanism before and after release of 24-hr ureteral obstruction in the presence or absence of postobstructive diuresis (bilateral or unilateral ureteral obstruction), and to examine the relationship between changes in interstitial pressure and TGF sensitivity.

Methods

Micropuncture experiments or clearance experiments with the measurement of interstitial hydrostatic and oncotic pressure were performed on male Sprague-Dawley rats weighing between 230 and 340 g under three different conditions: *(1)* 24 hr of complete unilateral ureteral obstruction (UUO), *(2)* 24 hr of complete bilateral ureteral obstruction (BUO), *(3)* sham-operated controls 24 hr postoperatively. To obstruct one or two ureters or to perform sham operation, we induced anesthesia

Received for publication June 7, 1983,
and in revised form January 24, 1984

with the intraperitoneal injection of Brevital, 50 mg per kilogram of body wt (Lilly International Corp.) and placed the animals on a servocontrolled heating table. After the operation the animals were allowed to awaken in their cages. Food and water was withheld from the BUO animals, but UUO and sham-operated animals were allowed free access to water until the start of the experiment 24 hr later. Anesthesia was induced by intraperitoneal injection of Inactin, 120 mg per kilogram of body wt (Byk, Konstanz, Federal Republic of Germany), rats were placed on a thermoregulated table, tracheostomy was performed, and 0.9% saline was infused via the right femoral vein at a rate of 1.5 ml/hr in UUO and sham-operated controls. BUO animals received 0.5 ml/hr before release and 2 ml/hr after release of obstruction. The right femoral artery was catheterized for continuous measurement of arterial blood pressure and sampling of plasma. The left kidney was exposed by a left subcostal flank incision and placed in a plastic cup; it was immobilized in isotonic agar/agar 3%. The surface of the kidney was covered with mineral oil.

The study protocol was as follows: Before release of ureteral obstruction measurements were made over 60 to 90 min (30-min periods); ureteral obstruction was then released by inserting a polyethylene catheter (PE 50) into the left renal pelvis and; after a 30-min nonsampling period, four 30-min postobstructive periods were obtained.

Micropuncture experiments

In the first series of experiments a servonulling pressure device (WP-Instruments, New Haven, Connecticut) was used to measure the stop-flow pressure (P_{SF}) in early proximal tubules of surface nephrons. This technique has been described previously by Schnermann, Persson, and Ågerup [4]. In our experiments the stop-flow situation was achieved by injecting a solid wax block into the early proximal tubule by a technique described by Gutsche et al [5]. A third micropipette connected to a calibrated type of microperfusion pump (Hampel, Frankfurt, Federal Republic of Germany) was used to perfuse the loop of Henle of the same nephron at different rates, 0 to 40 nl/min, with a modified Ringer solution (140 mM KCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 4 mM $NaHCO_3$, 7 mM urea, 2 g/liter lissamine green, pH 7.4). The stop-flow pressure was continuously recorded while the perfusion rate was being increased in steps of 2.5 to 5 nl/min. The maximal stop-flow pressure decrease (ΔP_{SF}) was measured at high perfusion rates and the turning point of the feedback (TP) was defined as the perfusion rate at which 50% of the maximal decrease in stop-flow pressure was obtained. In each nephron studied the stop-flow pressure response was determined at least twice. The order of perfusion was varied. Sometimes we started with a low and sometimes with a high perfusion rate. Usually both types were used in most nephrons. The same response was always obtained irrespective of if we started with low or high perfusion rate. Duration of flow was always long enough to obtain a stable pressure, usually taking 1 to 5 min to develop. The maximal stop-flow pressure was always the same after as before end-proximal microperfusion. In several nephrons in each group, the distal tubule was punctured and tubular fluid was collected during microperfusion to be certain that impaired delivery did not affect the stop-flow pressure response. The response was not altered by distal collections in any of the nephrons studied. Sampling of the tubular fluid to determine the proximal tubular fluid rate under free-flow conditions was accomplished by inserting a micropipette into the end-proximal segment of the nephron and collecting all the fluid above a distally placed oil block with constant monitoring of intratubular pressure in a more proximal segment. The collection was always made at the pre-existing pressure for at least 5 min. Care was taken to take samples from all nephrons irrespective of the pre-existing pressure level to avoid selection of nephrons.

In analysis of the stop-flow pressure response curves it has been found that the response occurs within a flow range of a few nanoliters per minute [6, 7], and that the turning point, that is, the inflection point of the sigmoid response curves, varies somewhat between individual nephrons. If the stop-flow pressure at different perfusion rates from individual nephrons is averaged, the mean response curve will flatten out due to differences in the turning point. If information from more than one nephron is desired to obtain the response curves, a normalization method affecting tubular flow, stop-flow pressure coordiates for each nephron was developed. In this way information from all nephrons in each rat group can be used to determine the shape of the response curve [8]. In this method the individual nephron data for perfusion rate (PR) and the corresponding stop-flow pressure (P_{SF}) was normalized to the mean values for maximal stop-flow pressure ($\overline{P_{SFmax}}$), maximal change in stop-flow pressure ($\overline{\Delta P_{SF}}$) and the turning point ($\overline{TP}$) in each situation. The formulas used for normalization of the stop-flow pressure (P_{SFn}) and the perfusion rate (PRn) are given below:

$$P_{SFn} = \overline{P_{SFmax}} - (P_{SFmax} - P_{SF}) \cdot \overline{\Delta P_{SF}}/\Delta P_{SF} \quad (1)$$

$$PRn = PR \cdot \overline{TP}/TP \quad (2)$$

These normalized data from all nephrons in one group of animals were then pooled and a curve was fitted to the following equation describing P_{SF} as a function of the perfusion rate using a curve-fitting program utilizing a nonlinear least-squares method (Minuite, Cern)

$$P_{SF} = P_{SFmin} + \frac{\Delta P_{SF}}{1 + e^{W\,(PR\,-\,TP)}} \quad (3)$$

where P_{SFmin} is the minimum value for stop-flow pressure at a high perfusion rate, ΔP_{SF} is the maximum change in stop-flow pressure, TP the turning point, and W a parameter determining the width of the perfusion interval for the stop-flow pressure response. To describe the curve, the following values can be calculated: *(1)* The interval for a decrease in P_{SF} from 10 to 90% of full response; *(2)* the slope of the steepest part of the curve. The formula for the interval is: $4 \cdot \tanh^{-1}(0.8)/W$ $(4.4/W)$. The formula for the slope is: $-\Delta P_{SF} \cdot W/4$.

Interstitial pressure parameters, clearances, and excretion data

In the second series of experiments, measurements of interstitial hydrostatic and oncotic pressure, urine flow rate, glomerular filtration rate (GFR), sodium excretion, potassium excretion, plasma protein concentration, and plasma creatinine concentration were performed in BUO, UUO, and sham-operated rats using the same experimental protocol as in the first series of micropuncture experiments.

Table 1. Micropuncture measurements and arterial blood pressure; sham-operated controls

	Before release of obstruction							*After* release of obstruction					
Rat	Pt	P_{SF}	TP	ΔP_{SF}	ΔP_{SF}%	Pa	Rat	Pt	P_{SF}	TP	ΔP_{SF}	ΔP_{SF}%	Pa
1	8	30	20	12	40.0		1	8	31	20	8	25.8	
	11	25	17.5	15	60.0	105		11	38	25	12	31.6	105
	8	31	17.5	10	32.3			12	30	20	7	23.3	
2	12	43	22.5	17	39.5		2	10	36	22.5	19	52.8	
	10	33	22.5	10	30.3	115		13	41	27.5	7	17.1	100
	11	33	22.5	12	36.4			12	37	27.5	11	29.7	
3	9	34	20	12	35.3		3	10	39	22.5	6	15.4	
	15	32	17.5	8	25.0	130		9	36	22.5	11	30.6	130
	16	28	12.5	12	42.9			14	36	22.5	7	19.4	
N	9	9	9	9	9			9	9	9	9	9	
Mean	11.1	32.1	19.2	12.0	37.7	117		11.0	36.0	23.3	9.7	27.3	112
SE	0.9	1.7	1.1	0.9	3.3	7		0.6	1.2	0.9	1.4	3.4	9
$P <$								NS	<0.01	<0.01	<0.01	<0.001	
$P^a <$	NS	<0.01	<0.001	<0.05	NS			NS	<0.01	<0.001	<0.05	NS	NS
$P^b <$	<0.01	<0.01	<0.05	<0.001	<0.01			NS	<0.01	<0.05	<0.001	<0.01	

Abbreviations: Pt (mm Hg), tubular pressure; P_{SF} (mm Hg), stop-flow pressure; TP (nl/min), turning point; ΔP_{SF} (mm Hg), maximal drop in P_{SF}; ΔP_{SF}%, percent change in stop-flow pressure; Pa (mm Hg), arterial pressure; *N*, number of nephrons.

[a] The values represent the significance tested between sham-operated controls and rats that had unilateral ureteral obstruction (UUO).

[b] The values represent the significance tested between sham-operated controls and rats with bilateral ureteral obstruction (BUO).

To collect renal lymph, a hilar lymph vessel was cannulated with a thin polyethylene catheter filled with heparin solution to prevent coagulation. All other visible lymph vessels proximal to the renal lymph node were tied off and lymph was collected in glass capillaries. It has been found previously by Wolgast et al [9] that protein concentration in collected hilar lymph closely resembles the values found in the subcapsular interstitial space.

To obtain a measurement of the interstitial hydrostatic pressure, the subcapsular hydrostatic pressure was continuously measured using a PVC catheter about 20 to 40 μm in diameter placed in the subcapsular space by a small incision in the renal capsule [10]. The hole in the capsule was completely sealed with Histoacryl®. The length of the catheter was adjusted to give a tip resistance of about 2 M ohm and the catheter was connected to a servonulling device. The pressure recordings had to fulfill two criteria to be considered accurate, namely a sharp rise in pressure after the sealing of the capsule and a high pressure recording when the renal vein was compressed at the end of the experiments. In the BUO group 9 of 11 animals, in the UUO group 7 of 8 animals, and in sham-operated controls 5 of 5 animals, fulfilled these criteria.

For GFR estimations an infusion of ^{51}Cr EDTA in 0.9% saline at a rate of about 10 μCi/hr was begun 30 min before the experiment. Blood samples were taken at the middle of each urine collection period. Urine and blood samples were analyzed in a multichannel gamma counter (ND 100, Nuclear Data Inc, Schaumburg, Illinois) and the clearance of ^{51}Cr EDTA was calculated. Urine volumes were measured by weighing. Urine osmolality was measured by freezing point depression (Knauer, Berlin, Federal Republic of Germany). Urinary concentration of sodium and potassium were determined by atomic absorption (Perkin-Elmer, Norwalk, Connecticut). No significant changes in the clearances and excretory data were seen during the postobstructive period; therefore, the values are the means for the whole period. Lymph and plasma protein concentration were determined according to Lowry et al [11] using human serum albumin as the standard, and plasma oncotic pressure calculated from these values according to the Landis-Pappenheimer equation [12].

Statistical analysis was performed using analysis of variance to compare groups; the Sheffe test was used to test the significance between the groups when a significant interaction was found. All values are shown as mean ± SE.

Results

In both the micropuncture and clearance series of experiments, arterial blood pressure (Pa) was significantly ($P < 0.05$) higher in the BUO animals than in sham-operated controls or UUO animals (Tables 1 to 4). The plasma creatinine levels did not change during the course of the experiments and were higher in the BUO group, 3.72 ± 0.5 mg · dl^{-1}, compared to 0.48 ± 0.1 mg · dl^{-1} in the UUO group, and 0.37 ± 0.1 mg · dl^{-1} in the controls. The mean body weight loss between the primary operation and start of the experiment was 3.4 ± 0.2, 4.8 ± 0.5, and 6.2 ± 1.5% for BUO, UUO, and controls, respectively. Kidney weights after finishing the experiments were 1.83 ± 0.08 g for BUO, and 2.05 ± 0.11 g for the left and right kidneys, respectively, for UUO, 1.60 ± 0.09 g (left, obstructed) and 1.24 ± 0.06 g, and for sham controls 1.15 ± 0.03 and 1.10 ± 0.06 g. The weight differences were significant for both kidneys of the BUO group ($P < 0.02$) and for the obstructed left kidney of the UUO group ($P < 0.01$) when compared to the sham-operated group.

Micropuncture experiments (Tables 1 to 3)

Proximal tubular pressure before the release of obstruction was similar in the control and UUO group (mean value 11.1

Table 2. Micropuncture measurements and arterial blood pressure, before and after the release of 24-hr unilateral ureteral obstruction (UUO)

	Before release of obstruction							*After* release of obstruction					
Rat	Pt	P_{SF}	TP	ΔP_{SF}	ΔP_{SF}%	Pa	Rat	Pt	P_{SF}	TP	ΔP_{SF}	ΔP_{SF}%	Pa
1	10	31	9	13	41.9		1	—	28	17.5	7	25.0	
	12	26	17.5	7	26.9	105		—	25	17.5	4	16.0	120
	11	26	15	6	23.0			11	30	7.5	7	23.3	
								19	32	12.5	4	12.5	
2	10	15	10	6	40.0	105	2	15	25	15.0	6	24.0	95
	10.5	20	10	5	25.0			12	28	12.5	6	21.4	
3	11	22	7.5	13	59.1	115	3	14	22	10	8	36.4	115
	18	32	7.5	15	46.9			10	37	7.5	18	48.6	
4	9	11	7.5	8	72.7	125	4						
	8	18	7.5	5	27.8			—	—	—	—	—	—
5	22	32	12.5	11	34.4	130	5	10	37	20	5	13.5	120
	16	24	10	6	25.0			10	31	15	4	12.9	
N	11	11	11	11	11			8	10	10	10	10	
Mean	12.5	23.4	10.4	8.6	38.4	116		12.6	29.5	13.5	6.9	23.4	113
SE	1.3	2.1	1.0	1.1	4.8	5		1.1	1.6	1.3	1.3	3.6	6
P <								NS	<0.01	<0.01	<0.01	<0.001	
P^a <	NS	NS	<0.001	NS	NS			NS	NS	<0.001	NS	NS	

Abbreviations are the same as those used for Table 1.
[a] The values represent the significance tested between UUO and BUO.

Table 3. Micropuncture measurements and arterial blood pressure before and after the release of 24 hr of bilateral ureteral obstruction (BUO)

	Before release of obstruction							*After* release of obstruction					
Rat	Pt	P_{SF}	TP	ΔP_{SF}	ΔP_{SF}%	Pa	Rat	Pt	P_{SF}	TP	ΔP_{SF}	ΔP_{SF}%	Pa
1	15	22	20	11	50.0	125	1	12	31	15	3.5	11.3	120
								12	34	27.5	5	14.7	
2	10	23	35	2	8.7	135	2	12	25	30	4.5	18.0	135
	22	31	20	7.5	24.2			22	33	27.5	8	24.2	
3	13	24	20	6.5	27.1	130	3	16	36	22.5	5	13.9	120
	21	27	20	10	37.0			15	41	27.5	3	7.3	
4	21	28	17.5	10	35.7	125	4	9	21	25	5.5	26.2	125
	18	35	17.5	10	28.6								
5	22.5	26	27.5	5	19.2		5	11	18	35	1	5.6	120
	22.5	27	30	3	11.1	145		9	21	40	0	0	
	30	—	—	—	—								
N	10	9	9	9	9			9	9	9	9	9	
Mean	19.5	27.0	23.0	7.2	27.2	132		13.1	28.9	27.8	3.9	13.4	124
SE	1.8	1.4	2.1	1.1	4.6	4		1.4	2.6	2.4	0.8	2.9	3
P								NS	<0.01	<0.01	<0.01	<0.001	

Abbreviations are the same as those used for Table 1.

and 12.5 mm Hg, respectively, Tables 1 and 2) and significantly higher for the BUO animals compared with controls (19.5 mm Hg, Table 3). Statistical comparisons between groups are shown in Tables 1 and 2. After the obstruction was released, the mean values were similar in all groups (11.0, 12.6, 13.1 mm Hg in sham, UUO, and BUO, respectively).

Maximal stop-flow pressure (P_{SFmax}) before the release was significantly decreased in both the UUO and BUO animals (23.0 and 27.0 mm Hg, respectively) when compared with controls (32.1 mm Hg). After the release of obstruction these differences persisted.

The activity of the TGF mechanism, as characterized by the *turning point* (TP, or point of 50% maximal activation) revealed a resetting for UUO. Before release of obstruction the TP in UUO was 10.4 nl/min which is significantly lower than both controls (19.2 nl/min) and BUO (23.0 nl/min). The turning point in BUO was slightly higher than control values. After the obstruction was released, TP was in all groups higher than be-

Table 4. Arterial blood pressure (Pa), hematocrit (Hct), lymph oncotic pressure (Π_L), and subcapsular hydrostatic pressure (P_{sc}) before and after the release of 24-hr ureteral obstruction (means ± SE)

	Before release			*After* release		
	Sham op controls (N = 5)	UUO (N = 7)	BUO (N = 9)	Sham op controls (N = 5)	UUO (N = 7)	BUO (N = 9)
Pa, *mm Hg*	108 ± 1.2	111 ± 2.6[b]	126 ± 1.9[a]	102 ± 1.2	106 ± 2.1[b]	126 ± 2.6[a]
Hct, *vol %*	46.7 ± 2.2	45.5 ± 0.7	46.6 ± 0.5	46.4 ± 1.1	44.6 ± 0.6	46.8 ± 0.4
Π_L, *mm Hg*	2.3 ± 0.6	6.3 ± 0.9[a,b]	3.6 ± 0.5	1.7 ± 0.3	5.9 ± 0.8[a]	4.4 ± 0.7[a]
P_{sc}, *mm Hg*	1.1 ± 0.4	1.9 ± 0.3[b]	3.8 ± 0.9[a]	1.1 ± 0.3	1.0 ± 0.4[b]	3.2 ± 0.9[a]
$P_{sc} - \Pi_L$, *mm Hg*	−1.2 ± 0.4	−4.4 ± 1.1[a,b]	0.1 ± 0.7	−0.7 ± 0.3	−4.9 ± 1.1[a,b]	−1.1 ± 0.8

Abbreviation: N, the number of animals.
[a] The value shown is significantly different from control rats ($P < 0.05$).
[b] The value shown is significantly different from BUO rats ($P < 0.05$).

fore and the TP in UUO (13.5 nl/min) remained significantly lower ($P < 0.001$) than control (23.3 nl/min) or BUO (27.8 nl/min), and in BUO the TP was higher than sham controls.

The maximum stop-flow pressure change (ΔP_{SF}) at high perfusion rates before the obstruction was released was less in UUO and BUO compared to controls; these differences remained after release. To compare stop-flow pressure responses in situations with different zero perfusion stop-flow pressure, the percentage change (stop-flow pressure response/stop-flow pressure at zero perfusion) seems more reasonable to use (ΔP_{SF}%). Before UUO was released, the ΔP_{SF}% was 38.4% compared with 37.7% in the sham-operated controls and 27.2% in the BUO (significantly different from control). After release the ΔP_{SF}% in the UUO was 23.4% (similar to controls 27.3%) and in BUO it was 13.4% significantly less than the control. Thus, the most consistent change, using ΔP_{SF}% or ΔP_{SF} was a decrease in the response after the release of BUO.

The feedback characteristics as calculated by the normalization method are shown as the curves from the curve fitting for the different situations before and after the obstruction was released in Figures 1 and 2.

To investigate whether the feedback mechanism was activated in the different situations studied, the end-proximal fluid flow rate (EPFR) was measured in a few animals. In the sham-operated controls there was no difference between early and late control periods. Therefore, a mean value for all observations was made and found to be 19.5 ± 2.4 nl/min (N = 12). Both in the control, the obstructed, and the postobstructed animals there was a wide range of flow rate estimations. Before release in UUO kidneys the flow rate was only 7.0 ± 1.8 nl/min (N = 9) but after release of obstruction, a mean value of 10.1 ± 1.9 nl/min (N = 6) was found. In the BUO kidneys values of 8.3 ± 2.4 nl/min (N = 7) and after release 11.0 ± 1.1 nl/min (N = 10) were found.

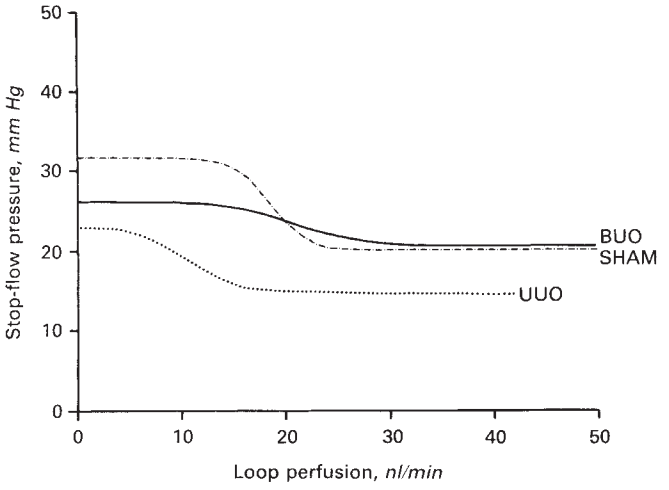

Fig. 1. *The tubular stop-flow pressure at different rates of tubular perfusion.* The *curves* are the result from fitting on normalized data from sham-operated controls, unilateral ureteral obstruction (UUO), and bilateral ureteral obstruction (BUO) before the release of 24-hr ureteral obstruction.

Clearance and excretory data (Table 5)

GFR was greatly reduced in both UUO and BUO kidneys. A significant difference was not detected between these two groups (Table 5). After the obstruction was released in the BUO kidneys, there was a pronounced postobstructive diuresis and natriuresis; potassium excretion in the BUO animals was similar to the control kidneys. In the postobstructive UUO animals there was no diuresis or natriuresis, and potassium excretion was lower than controls.

Interstitial hydrostatic and oncotic pressure (Table 4)

Subcapsular hydrostatic pressure (P_{sc}) was higher in the BUO animals which was a significant change both before and after release (Table 4). The effect of obstruction released on P_{sc} in BUO and UUO was slight. The lymph oncotic pressure (Π_L) was significantly increased in the UUO animals, before obstruction released could be compared to BUO or controls. From the hydrostatic pressure recordings and the lymph oncotic pressure calculations, a combined interstitial pressure difference could be calculated by subtracting interstitial oncotic pressure from the hydrostatic pressure ($P_{sc} - \Pi_L$, Fig. 3). From Table 4 and Figure 3 it may be seen that this net interstitial pressure difference in the controls was −1.2 ± 0.4 mm Hg before release and −0.7 ± 0.3 mm Hg after release. In UUO it was significantly lower (−4.4 ± 1.1 mm Hg) than control values, mainly due to the increased oncotic pressure, but in BUO the value (−0.1 ± 0.6 mm Hg) was not significantly

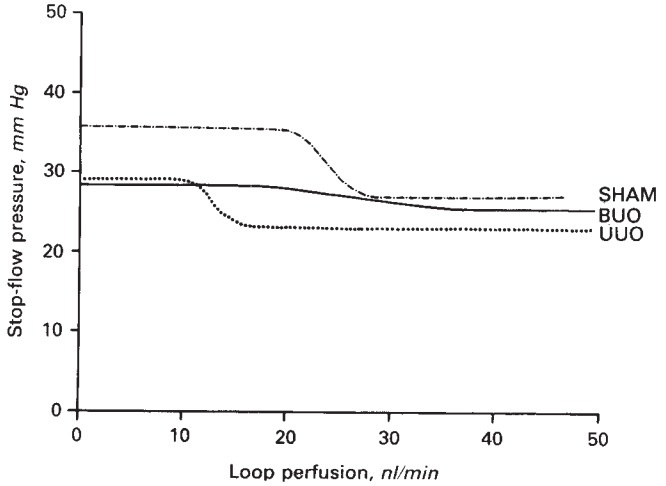

Fig. 2. *The tubular stop-flow pressure at different rates of tubular perfusion.* The *curves* are the result from fitting on normalized data from sham-operated controls, unilateral ureteral obstruction (UUO), and bilateral ureteral obstruction (BUO) after the release of 24-hr ureteral obstruction.

different from control. After the obstruction was released, the same pattern was seen with significantly lower combined interstitial pressure, $P_{sc} - \Pi_L$, in the UUO group compared to control or BUO, and with BUO not significantly different from control.

Plasma protein and hematocrit levels

The hematocrit was not different among the three groups and did not change after the obstruction was released (see Table 4). Plasma protein concentration showed a tendency to decrease after the obstruction was released. In UUO the concentration was 5.43 ± 0.14 g · dl^{-1} before the release. One and two hours after the release the values were 5.21 ± 0.14 and 4.91 ± 0.14, respectively. The difference between the concentration before and 2 hr after the release was significant ($P < 0.05$). In BUO the concentration before release, 1 and 2 hr after the release was 6.27 ± 0.17, 6.01 ± 0.13, and 6.15 ± 0.16 g · dl^{-1}, respectively. The corresponding values for sham-operated controls were 5.46 ± 0.16, 5.32 ± 0.20, and 5.14 ± 0.25 g · dl^{-1}, respectively. In BUO animals, the plasma protein concentration was significantly ($P < 0.02$) higher before, 1 and 2 hr after release than either controls or UUO. No significant difference between controls and UUO was found. Since the sum of plasma oncotic pressure and stop-flow pressure probably reflects glomerular capillary pressure and since P_{SFmax} was not different in BUO and UUO (Table 5), it is likely that glomerular capillary pressure was higher in BUO than UUO, both before and after the release of obstruction.

Discussion

The present results clearly demonstrate that both the activity of tubuloglomerular feedback control and renal interstitial pressure are different in the UUO and the BUO experimental models.

Unilateral ureteral obstruction

Tubuloglomerular (TGF) sensitivity was enhanced before and after the release of 24-hr unilateral ureteral obstruction (UUO) as indicated by the significant decrease in the *turning point*, that is, the tubular perfusion rate at which 50% of the maximal decrease in stop-flow pressure occurred (Table 2). This decrease in the turning point of TGF is graphically demonstrated using the normalized curves describing TGF in which UUO responses are significantly shifted to the left compared to either sham-operated or BUO rats (Figs. 1 and 2). The finding of enhanced TGF sensitivity before the release of 24-hr UUO is in marked contrast to the decrease in sensitivity, in fact the absence of TGF response, before the release of 1- to 2-hr UUO [13]. In this early phase of ureteral occlusion (2 hr) there is a marked renal vasodilation and increased interstitial hydrostatic pressure that parallels the observed reduction in feedback sensitivity. Later in the course of UUO there is an increased vasoconstriction that reduces intratubular pressure despite obstruction [14]. By 12 to 24 hr the feedback response obviously has returned as shown in the present study and in studies on single nephron obstruction [15].

Earlier studies indicate that interstitial hydrostatic and oncotic pressure conditions are important modulators of the sensitivity of the TGF mechanism [3]. During dehydration [10], renal hypotension [16], or after release of 2 hr of UUO [13], TGF sensitivity increases in association with a high interstitial oncotic pressure, a decrease in interstitial hydrostatic pressure or both. In the 24-hr UUO kidney a high interstitial oncotic pressure was found that could be responsible for the increased sensitivity of the TGF mechanism.

Enhanced TGF sensitivity could contribute significantly to the altered physiology of the UUO kidney. It is probable that the feedback mechanism was activated in some nephrons in the UUO after release, although not in all, since the measured tubule fluid flow rate was similar to the turning point, or point of half-maximal TGF activation. Activation of the TGF mechanism could restrain the increase in GFR after release of UUO. The increase in interstitial oncotic pressure may be involved in the increased fractional reabsorption of sodium and water described in the proximal tubule of the postobstructive UUO kidney [17]. Taken together these changes result in decreased delivery of filtrate to the distal nephron and collecting ducts where decreased tubular reabsorption is observed [18]. Thus, the changes in interstitial pressure and TGF sensitivity may partially explain the lack of postobstructive diuresis after the release of unilateral ureteral obstruction.

Bilateral ureteral obstruction

After relief of 24-hr bilateral ureteral obstruction a marked postobstructive diuresis was observed (Table 5), as noted previously. Tubuloglomerular feedback sensitivity as indicated by the turning point was significantly decreased in the BUO kidney both before and after the release of obstruction and a blunted TGF sensitivity was also suggested by the relatively small decrease in stop-flow pressure response ($\Delta P_{SF}\%$) occuring at high flow rates. As shown in Tables 1 to 3, the $\Delta P_{SF}\%$ decreased only 13.4 ± 2.9% after the release of BUO but decreased 27.3 ± 3.4% in sham controls ($P < 0.01$) and 23.4 ± 3.6% in UUO (not significantly different). The normalized

Table 5. Excretory data for control, UUO, and BUO rats before and after the release of 24-hr ureteral obstruction

		V_u *μl/min*	GFR *ml/min*	$[Na^+]_u$ *mmoles/liter*	Na^+ excr *μmoles/min*	$[K^+]_u$ *mmoles/liter*	K^+ excr *μmoles/min*
Before release							
Control	l k	3.2 ± 0.8	1.36 ± 0.12	37 ± 9	0.14 ± 0.06	312 ± 34	0.94 ± 0.18
(*N* = 5)	r k	3.0 ± 0.3	1.24 ± 0.16	40 ± 7	0.12 ± 0.02	270 ± 43	0.81 ± 0.14
UUO (*N* = 8)	r k	5.4 ± 0.6	1.95 ± 0.27	73 ± 16	0.48 ± 0.1	195 ± 20	1.00 ± 0.14
After release							
Control	l k	3.7 ± 1.1	1.44 ± 0.10	90 ± 15	0.36 ± 0.13	299 ± 45	0.91 ± 0.06
(*N* = 5)	r k	3.4 ± 0.4	1.63 ± 0.17	63 ± 10	0.23 ± 0.05	279 ± 10	0.95 ± 0.08
UUO	l k	3.1 ± 0.6	0.24 ± 0.07[a]	84 ± 11	0.29 ± 0.07	50 ± 9	0.14 ± 0.03[a]
(*N* = 8)	r k	6.6 ± 0.8	2.21 ± 0.3	150 ± 24	0.95 ± 0.16	197 ± 11	1.26 ± 0.12
BUO (*N* = 11)	l k	29.3 ± 3.2[a,b]	0.16 ± 0.02[a]	98 ± 5	2.90 ± 0.37[a,b]	37 ± 4	1.06 ± 0.14[b]

Abbreviations: V_u, means ± SE for urine flow rate; GFR, glomerular filtration rate; $[Na^+]_u$, $[K^+]_u$, concentrations of sodium and potassium in urine; Na^+ excr, K^+ excr, urinary excretion of sodium and potassium from left kidney (l k) and right kidney (r k); *N*, the number of animals.

[a] The value represents a significant difference from control rats ($P < 0.05$).

[b] The value represents a significant difference from rats with unilateral ureteral obstruction (UUO; $P < 0.05$).

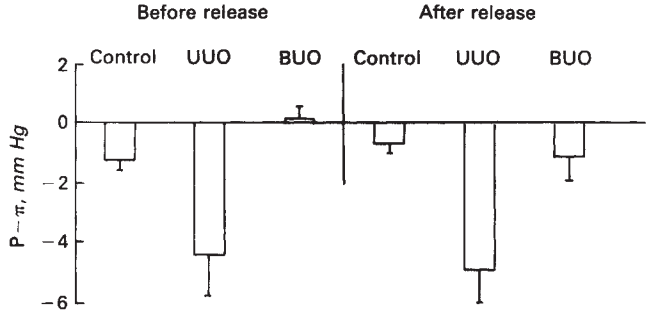

Fig. 3. *Combined interstitial pressure calculated as* (P − Π) *in sham-operated control, unilateral ureteral obstruction (UUO), and bilateral ureteral obstruction (BUO) rats before and after the release of 24-hr ureteral obstruction.*

curves of TGF response illustrate this decrease in TGF sensitivity by the wide interval and relatively flat slope in BUO (Figs. 1 and 2). Lack of activation of TGF mechanism in the BUO kidney is also indicated by the proximal tubular fluid flow rates which were much below the turning point of the TGF response. The changes in combined interstitial pressure parameters in BUO kidneys were not remarkable (Table 4). Interstitial hydrostatic pressure (P_{sc}) was increased before the obstruction was released, as expected in association with the high intratubular pressure, and lymph colloid osmotic pressure was also slightly increased, although not significantly before release, resulting in no change in net interstitial forces compared to control. During postobstructive diuresis after the release of BUO, the interstitial lymph colloid osmotic pressure was increased and hydrostatic pressure also remained slightly increased so that again no change in the net interstitial Starling force was seen. Thus, the blunting of glomerular stop-flow pressure response to increased distal flow in BUO kidneys was not associated with the increase in interstitial hydrostatic pressure and the decrease in colloid oncotic pressure observed with the reduced TGF sensitivity during isotonic volume expansion [19].

Other factors that can contribute to the resetting process must be considered. The beneficial effect of inhibition of angiotensin-II-formation on the vasoconstriction of UUO kidney [20] reports a possible role for this hormone system to mediate changes in TGF sensitivity.

Adenosine is another potent intrarenal vasoconstrictor agent which Osswald, Hermes, and Nabakowski [21] show may be involved in the signal transmission of the TGF mechanism. Moreover, adenosine concentration is increased in the UUO kidney and theophylline, an adenosine antagonist, increased GFR after UUO [22].

Renal prostaglandin synthesis is enhanced in the hydronephrotic kidney [23]. Vasoconstrictor prostaglandins (thromboxanes) appear to predominate in the 24-hr UUO kidney [20], and thromboxane synthesis in the cortex of such kidneys is increased [24]. The status of prostaglandin synthesis in the BUO kidneys is less well studied, but such kidneys have a blunted response to vasoconstrictors such as norepinephrine and angiotension [25] and a higher glomerular capillary pressure, as discussed above. Indomethacin prevents the increase in renal blood flow and intratubular pressure during the first 4 hr of BUO [26].

The findings of the present study may be important in further understanding the intrarenal mechanisms contributing to postobstructive diuresis. The lack of significant change in net interstitial Starling forces in the BUO kidney may mean reduced tubular reabsorption in BUO compared to UUO where increased interstitial colloid oncotic pressure was seen. The reduced response of P_{SF} to increased distal flow suggests a higher glomerular capillary pressure at a given tubular flow rate after the release of BUO compared to UUO and, taken together, these changes would result in a relative increase in delivery of filtrate to the distal nephron and collecting ducts. Further evidence of higher glomerular capillary pressure (P_{GC}) in BUO compared to UUO is provided by the finding of increased

plasma colloid oncotic pressure in BUO which, when combined with similar P_{SFmax} values, results in higher estimated glomerular capillary pressure. Directly measured P_{GC} was found to be higher in BUO than UUO before and after release of 24 hr obstruction by Dal Canton et al [14, 27]. Afferent arteriolar conductance and blood flow was normal in BUO and reduced in UUO, findings entirely compatible with lack of TGF activation in the former and increased sensitivity in the latter. After release of bilateral ureteral obstruction, Dal Canton et al [27] noted an increase in afferent arteriolar resistance and postulated that increased delivery of sodium chloride to the distal nephron might activate TGF. However, our results do not support this suggestion since TGF was not activated after the release of BUO.

Summary

The present investigation shows that after 24 hr of ureteral occlusion there is a feedback response at increased distal delivery of fluid with a high sensitivity in the UUO and a low sensitivity in a BUO-situation. One factor of importance for this resetting seems to be changes in interstitial, hydrostatic, and oncotic pressures but other factors may also contribute. Furthermore, the TGF system seems to be activated in some nephrons in the UUO-kidney but in not the BUO-kidney. These findings may possibly explain the phenomenon of post-obstructive diuresis that occurs after release of 24 hr of BUO but not after release of 24 hr of UUO.

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