outer cortical regions with ipsilateral CPUO in Group I suggests the action of circulating vasoconstrictors. In contrast, distribution of RBF to inner cortical regions following uninephrectomy and severe CPUO in Group II may be due to the opposing actions of vasodilators. A better understanding of the factors underlying changes in glomerular perfusion patterns during CPUO in early development may lead to better preservation of renal function in infants with congenital obstructive nephropathy.

Acknowledgments. Ms. Jean De Piro provided secretarial assistance.

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0031-3998/84/1812-1271$02.00/0
PEDIATRIC RESEARCH
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Vol. 18, No. 12, 1984
Printed in U.S.A.

Chronic Partial Ureteral Obstruction in the Neonatal Guinea Pig. II. Pressure Gradients Affecting Glomerular Filtration Rate

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ABSTRACT. Neonatal guinea pigs with chronic partial ureteral obstruction (CPUO) and contralateral nephrectomy develop hydroureteronephrosis and reduced glomerular filtration rate (GFR) without significant reduction of renal blood flow. To investigate the role of pressure gradients in determination of GFR, micropuncture studies were performed in animals 23 ± 3 days of age subjected to left ureteral constriction and right nephrectomy within the first 2 days of life and compared to uninephrectomized controls. Resulting ureteral dilatation was variable, with kidney weight and ureteral diameter being proportional to the rise in ureteral pressure (P_U). In individual animals with severe CPUO (ureteral diameter ≥ 3 mm), distal tubular transit time was either normal (31–90 s) or prolonged (>120 s). Superficial single nephron GFR (SNGFR) was inversely correlated with P_U.

Glomerular capillary pressure and afferent arteriolar colloid oncotic pressure were not affected by CPUO while peritubular capillary, proximal and distal intratubular hydrostatic pressure increased as a function of P_U. As a result, afferent effective filtration pressure (EFP_A) was reduced in severe (10.0 ± 1.1 mm Hg) compared to mild CPUO (13.4 ± 0.5 mm Hg), but was not different from controls (11.3 ± 0.9 mm Hg). For both control and CPUO groups,

Received March 12, 1984; accepted May 22, 1984.

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This work was supported by National Institutes of Health Grant 5 S07 RR 05431-21, by a Grant-in-Aid from the American Heart Association, and with funds contributed in part by the American Heart Association, Virginia Affiliate. R.L.C. is an Established Investigator of the American Heart Association. This study was presented in part at the Second International Workshop on Developmental Renal Physiology, Marburg, West Germany, August 27, 1983, and at the 6th International Pediatric Nephrology Symposium, Hanover, West Germany, September 1, 1983.

superficial SNGFR increased by 0.5 nl/min for each mm Hg increase in EFP_A but for a given EFP_A, SNGFR was 6 nl/min lower in guinea pigs with CPUO. These results indicate that higher EFP_A in animals with mild compared to severe CPUO contributes to maintenance of higher SNGFR. However, a 70% reduction in superficial SNGFR for guinea pigs with severe CPUO is due in large part to reduced ultrafiltration coefficient. The mechanisms whereby chronically elevated P_U in the neonate result in these complex changes of glomerular dynamics may relate to altered intrarenal production of vasoactive hormones. (*Pediatr Res* 18:1271–1277, 1984)

Abbreviations

CPUO, chronic partial ureteral obstruction
EFP_A, afferent effective filtration pressure
GFR, glomerular filtration rate
P_{DT}, distal intratubular hydrostatic pressure
P_{GC}, glomerular capillary pressure
P_{PT}, proximal intratubular hydrostatic pressure
P_{SF}, stop-flow pressure
P_U, intraureteral pressure
SNGFR, single nephron glomerular filtration rate

Unilateral chronic partial ureteral obstruction in the neonatal guinea pig results in hemodynamic changes which are dependent on the severity of obstruction and influenced by the presence or absence of the contralateral kidney (6). Unlike animals with the opposite kidney in place, in which severe CPUO results in elevated renal vascular resistance, those uninephrectomized at birth have little decrease in renal blood flow although GFR was reduced by approximately 50% (6). Because these guinea pigs have marked hydroureteronephrosis suggesting increased intraureteral hydrostatic pressure, the present study was designed to evaluate the role of pressure gradients influencing GFR in this model. As animals with contralateral nephrectomy and severe CPUO were azotemic despite compensatory renal hypertrophy, this group was chosen for further study because functional adaptation to CPUO would be expected to be maximal in an effort to maintain homeostasis.

While previous studies of glomerular dynamics during CPUO have been performed in adult rats with mild ureteral obstruction and intact contralateral kidney (13, 22), there are no published reports of glomerular dynamics in CPUO during early development. The guinea pig was chosen for the present experiments because like the human, all nephrons are formed at the time of birth and functional maturation of the superficial nephrons is normally accelerated during the 3rd and 4th weeks of life (3, 21). This process is further augmented by uninephrectomy at birth (2–4). Micropuncture techniques were used to examine superficial single nephron function during this dynamic period in which the kidney was responding to the combined influence of rapid somatic growth, reduced renal mass, and CPUO.

MATERIALS AND METHODS

Thirty-six Hartley guinea pigs were anesthetized with halothane within the first 48 h of life. All animals were subjected to right nephrectomy and in 28 guinea pigs a 2-mm length of PE60 polyethylene tubing was placed around the distal third of the left ureter. The ureter was left untouched in remaining guinea pigs to serve as controls. At 18–30 days of age, animals were anesthetized with intraperitoneal sodium pentobarbital, 3 mg/100 g body weight and placed on a thermostatically controlled heating table. Tracheostomy was performed, and 0.9% saline was infused through a jugular vein at 0.3 ml/100 g body weight. Forty-five min before beginning tubular fluid collections, [^{3}H]inulin (New England Nuclear, Boston, MA) was added to the saline infusate in a concentration of 100 μCi/ml. Donor guinea pig plasma was infused through the contralateral jugular vein at 0.9 ± 0.1 ml/h, adjusted to maintain constant hematocrit (2). Blood pressure was continuously monitored by means of a Statham 23ID pressure transducer connected to a carotid artery catheter.

The left kidney was prepared for micropuncture as previously described for this laboratory (2), and was bathed in 0.9% saline maintained at 39 ± 0.5° C. During maintenance of euvolemia as described above, external ureteral diameter was measured halfway between kidney and bladder using calipers under microscopic visualization. A flared polyethylene cannula was sutured into the bladder for collection of urine in a small weighed cup. As a result of urinary sediment formation, five animals developed acute complete ureteral obstruction during surgical preparation. In these guinea pigs, a fine PE10 polyethylene tube was threaded into the ureter such that the tip lay proximal to the stenosis, allowing urinary flow during the experiment. The resistance to urine flow through the cannula (0.70 ± 0.36 mm Hg/ml min^{-1}) was not different from that in remaining guinea pigs with CPUO (0.42 ± 0.10 mm Hg/ml min^{-1}) and results were therefore combined. Two to four serial timed urine collections, approximately 30 min each, were obtained throughout the experiment. Blood samples (100 μl) were drawn from the arterial catheter at the beginning and end of each urine collection period and were replaced by an equal volume of donor blood. Hematocrit was measured in heparinized capillary tubes.

In each animal, five to eight superficial proximal and distal convoluted tubules were identified by intratubular injection of FD & C green dye using sharpened 2-μm micropipettes. Distal tubular transit time was measured from the time of disappearance of dye from the last visible loop of a proximal tubule to the time of reappearance in the first superficial distal tubular segment. Free flow hydrostatic pressure was then measured in identified proximal (P_{PT}) and distal tubules (P_{DT}) as well as in adjacent peritubular capillaries (P_C) using a servo-nulling apparatus and sharpened 2- to 4-μm micropipettes containing 2 M NaCl. Using sharpened 8–10-μm siliconized micropipettes, two to six timed tubular fluid collections were then obtained from last accessible proximal tubular loops identified by dye injection by maintaining an oil block in constant position as previously described (2). Intratubular hydrostatic pressure was monitored during tubular fluid collection by means of a second 2–4-μm micropipette inserted upstream. As initiation of tubular fluid collection almost always resulted in decreased intratubular pressure, counterpressure was applied to the collection pipette to maintain the original pressure in approximately half of the measurements. In guinea pigs with severe ureteral obstruction, superficial proximal tubules varied from normal-appearing to grossly distended with diameters twice the normal size. In these animals, an attempt was made to obtain tubular fluid collections from both types of tubules, identified by distal transit time less than or ≥120 s. Stop-flow hydrostatic pressure was then measured in the same nephrons in the first accessible loop of the proximal tubule using a 2–4-μm micropipette while a second micropipette with outer diameter of 12–15 μm, containing Sudan black-stained castor oil, was used to block tubular fluid flow for 2–3 min. Intraureteral pressure was then measured proximal to the stenosis using an 8–10-μm micropipette. Penetration of the pipette tip into the ureteral lumen was ascertained by appearance of typical peristaltic pressure waves on the graphic record. Mean intraureteral pressure was measured between peristaltic peaks. The kidney was decapsulated, drained, weighed, and bisected. Half of the kidney was fixed in 10% formalin solution while the remaining half was dried at 40° C for 10 days for calculation of dry/wet ratio.

The volume of tubular fluid collections was measured using a filar eyepiece micrometer (Gaertner, Chicago, IL) after the sample was transferred to a constant-bore capillary tube. Samples of plasma, urine, and tubular fluid were placed in vials containing 0.5 ml water and 5 ml PCS solubilizer (Amersham/Searle) for

counting of ^3H in a liquid scintillation spectrometer (Beckman Instruments, Fullerton, CA). Plasma protein concentration was measured by the Lowry technique (19).

Calculations. Superficial SNGFR was calculated as SNGFR = $(TF/P)_{in} \times V_{TF}$ where $(TF/P)_{in}$ is tubular fluid-to-plasma inulin concentration ratio and V_{TF} is tubular fluid flow rate.

Afferent arteriolar colloid oncotic pressure was calculated from the measured plasma protein concentration using the relationship derived by Landis and Pappenheimer (18). Glomerular capillary pressure, afferent hydrostatic pressure gradient for ultrafiltration, and afferent effective filtration pressure were calculated as described previously (5).

Ureteral resistance was calculated as $R_U = P_U/V$ where V = urine flow rate.

Statistical analysis. Comparison between groups was performed by two-way analysis of variance and Duncan's multiple range test. Comparison of measurements of SNGFR with or without counterpressure, was evaluated by Student's t test for paired data. Linear regression analysis was performed by the method of least squares. Using a linear model (S.A.S. Institute, Cary, NC), the response characteristics of SNGFR to change in EFP_A were examined for CPUO and uninephrectomy control groups (17). Components of the model tested were group effects (treatment group), linear effects (variation with EFP_A), and difference of slopes between groups. Comparison of the distribution of distal transit time between groups was accomplished by the Mann-Whitney test statistic.

RESULTS

As shown in the *top panel* of Figure 1, somatic growth was impaired in proportion to the rise of intraureteral pressure, which varied from 0 to 16 mm Hg although uniform ureteral constriction was initially produced in each animal. Wet kidney weight increased linearly with intraureteral pressure, and because dry/wet kidney weight ratio was constant at approximately 0.2 for all animals with CPUO, the relationship was similar for dry kidney weight ($r = 0.55$, $p < 0.01$). Ureteral diameter proximal to the stenosis correlated closely with intraureteral pressure, which in turn reflects intrapelvic pressure. Animals with ureteral diameter less than 3 mm were classified as "mild CPUO." Guinea pigs with ureteral diameter of at least 3 mm had visible dilatation of the renal pelvis, a tortuous, convoluted ureter, and were classified as "severe CPUO."

Although tubular diameter was not quantitated, inspection of the kidney surface revealed that tubules with transit time exceeding 120 s were invariably more dilated than adjacent tubules with shorter transit time. As shown in Figure 2, 74% of distal transit times in the control group fell between 31 and 90 s. Surprisingly, while 80% of transit times in the mild CPUO group were in the same range, median transit time was 57.5 s compared to 66.0 s in controls ($p < 0.05$). In severe CPUO, 50% of transit times were greater than 120 s, while 45% were 31 to 90 s.

There was no difference in initial hematocrit between control (41.1 ± 0.7) and CPUO (40.3 ± 0.6) groups. At the end of the experiment, hematocrit was 40.4 ± 1.6 in control and 39.3 ± 0.8 in CPUO groups. Plasma inulin concentration varied 16.6 ± 3.5% between first and last blood samples. Plasma total protein concentration was not different between groups, averaging 5.40 ± 0.12 and 5.06 ± 0.13 g/dl in control and CPUO groups, respectively. Variability in urine flow between first and last urine collections averaged 17.1 ± 3.0%. Urine flow was 15.6 ± 5.2 μl/min in control animals and 14.1 ± 2.4 μl/min in those with ureteral obstruction (not significant), while resistance to urine flow was 0.02 ± 0.02 and 0.49 ± 0.11 mm Hg/μl min^{-1} in control and CPUO groups, respectively ($p < 0.05$). Although microscopic examination revealed no leukocytes or bacteria, a cloudy sediment of amorphous crystals was present in the urine of animals with ureteral obstruction. The sediment was most concentrated in the group with severe CPUO.

As shown in Figure 3, mean superficial SNGFR measured

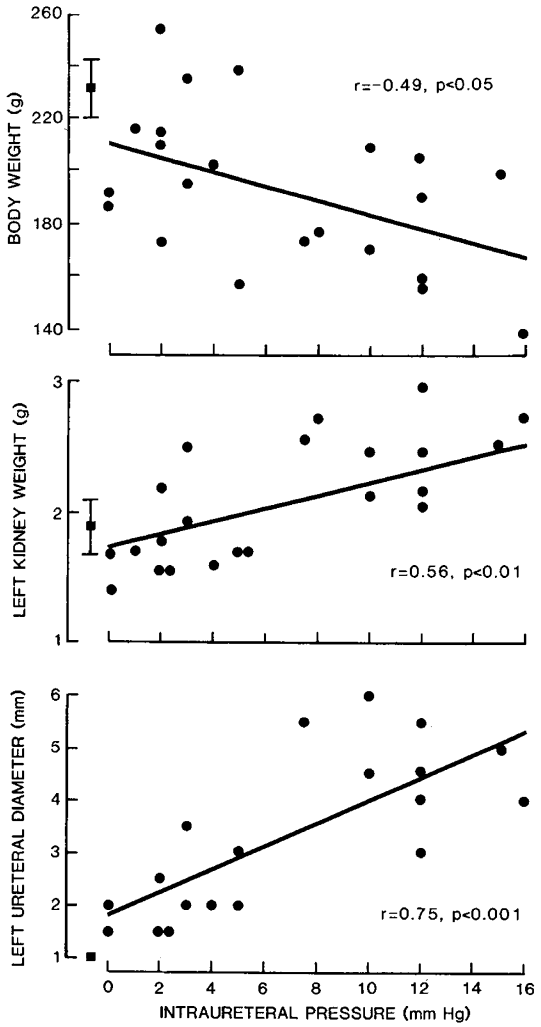

Fig. 1. *Top panel*: body weight *versus* intraureteral pressure; $y = -2.81x + 211$. *Middle panel*: left kidney weight *versus* intraureteral pressure; $y = 0.05x + 1.73$. *Lower panel*: left ureteral diameter *versus* intraureteral pressure; $y = 0.22x + 1.81$. ●, values for animals with CPUO and the *regression line* is for all animals with CPUO. ■, mean ± SE for control uninephrectomized animals.

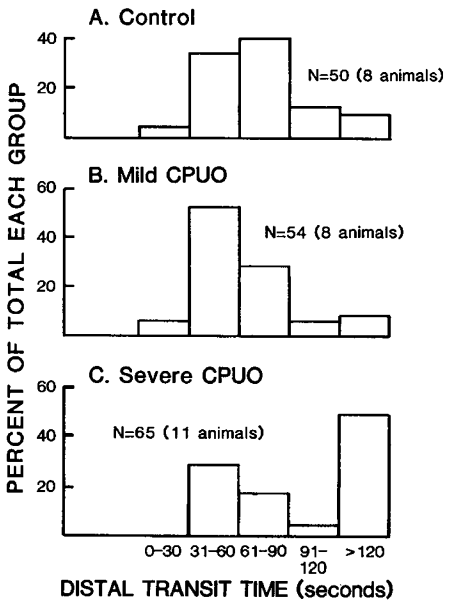

Fig. 2. Distal transit time for each group. N, number of observations in each group.

during maintenance of initial P_T was inversely correlated with intraureteral pressure. Due to technical difficulties in obtaining at least two tubular fluid collections during application of counterpressure in nephrons previously subjected to micropressure measurements, only 11 animals are represented in the experimental group. In both control and CPUO groups, SNGFR was significantly higher when tubular fluid was collected by free flow than during maintenance of initial P_{PT} by counterpressure ($p < 0.001$) (Table 1). Paired determinations of SNGFR with and without counterpressure by recollection from the same nephron in three control and three CPUO animals revealed a difference in SNGFR of 3.0 ± 0.7 nl/min ($n = 8$ pairs, $p < 0.001$), and in P_{PT} of 4.7 ± 0.6 mm Hg ($p < 0.001$). The $(TF/P)_{in}$ ratio was not different during free flow collections betweeen control (1.38 ± 0.07) and CPUO (1.36 ± 0.06) groups. Furthermore, there was no effect of counterpressure on $(TF/P)_{in}$.

The effect of P_{PT} to oppose filtration was thus more marked in severe CPUO wherein P_{PT} as well as P_{DT} were increased at P_U greater than 5 mm Hg (Table 1, Fig. 4). There was no effect of increasing P_U on either mean arterial pressure or glomerular capillary pressure, but peritubular capillary pressure was significantly correlated with severity of CPUO (Fig. 4). To determine

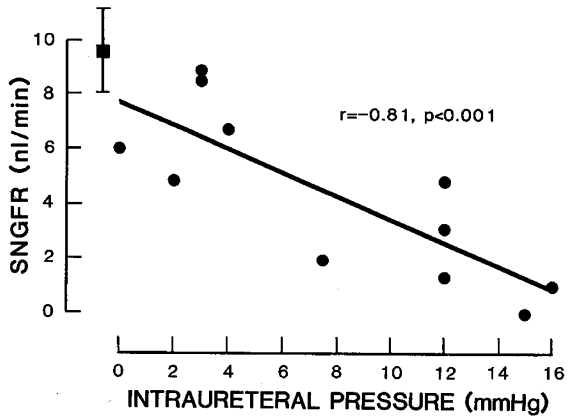

Fig. 3. Single nephron glomerular filtration rate measured during maintenance of initial proximal intratubular hydrostatic pressure, as a function of intraureteral pressure; $y = -0.43x + 7.68$. ●, mean of two to eight determinations for one animal with CPUO and the *regression line* is for animals with CPUO. ■, mean ± SE for control uninephrectomized animals.

Table 1. *Micropuncture data**

	Control uninephrectomy	Mild CPUO	Severe CPUO
SNGFR (nl/min)			
With counterpressure	9.63 ± 1.55 (5)	8.21 ± 1.72 (5)	2.99 ± 1.11† (7)
No counterpressure	13.39 ± 1.42 (5)	9.77 ± 1.75 (5)	5.11 ± 1.32† (5)
Pressure (mmHg)			
Mean arterial	62.9 ± 2.5	62.6 ± 2.3	63.6 ± 2.9
Glomerular capillary	38.7 ± 0.8	39.3 ± 1.4	39.6 ± 1.4
Proximal tubule	10.5 ± 0.4	10.0 ± 0.4	13.8 ± 0.4†‡
Distal tubule	7.3 ± 0.3	8.6 ± 0.7	10.5 ± 0.4†‡
Peritubular capillary	4.5 ± 0.2	4.7 ± 0.2	5.3 ± 0.4
Ureteral	0.1 ± 0.1	2.1 ± 0.5	10.2 ± 1.1†‡
Afferent effective filtration pressure	11.3 ± 0.9 (8)	13.4 ± 0.5 (10)	10.0 ± 1.1‡ (12)

* Values are mean ± SE (number of animals in parentheses).
† $p < 0.05$ *vs.* control.
‡ $p < 0.05$ *vs.* mild CPUO.

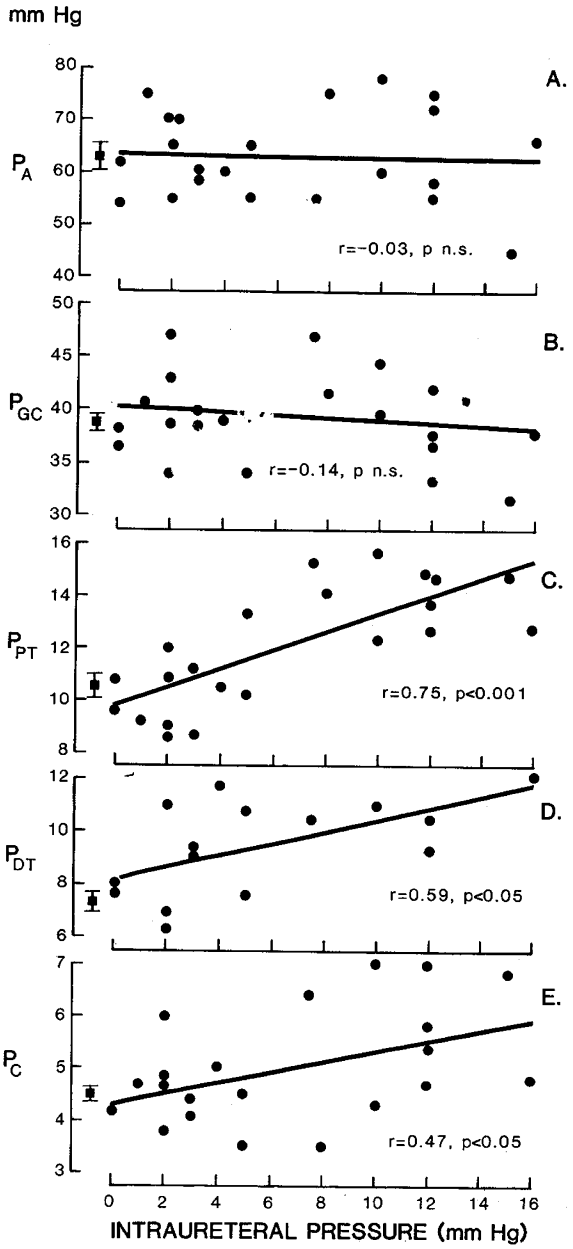

Fig. 4. Hydrostatic pressure determinations *versus* intraureteral pressure. *A*, P_A; $y = 0.05x + 63$. *B*, P_{GC}; $y = -0.12x + 40$. *C*, P_{PT}; $y = 0.34x + 9.8$. *D*, P_{DT}; $y = 0.22x + 8.2$. *E*, P_C; $y = 0.10x + 4.3$. *Symbols are the same as in Figure 3.*

whether prior tubular fluid collection altered P_{SF} measurement in the same nephron, deteminations of P_{SF} pressure in nephrons both with and without prior tubular fluid collection were made in nine guinea pigs with CPUO. The result did not differ between nephrons with previous tubular fluid collection (P_{SF} = 21.5 ± 1.0 mm Hg) and those without (22.2 ± 1.2 mm Hg).

Oncotic and hydrostatic pressure gradients affecting glomerular ultrafiltration are shown in Figure 5. Afferent colloid oncotic pressure did not change as a result of CPUO, while the transcapillary hydrostatic pressure gradient (and consequently EFP_A) was reduced in animals with severe CPUO. The relationship of SNGFR to EFP_A for each group is shown in Figure 6. There is a significant correlation between the two variables in control and CPUO groups, and the slope does not differ between groups. However, the y axis intercept of the regression line is 6 nl/min higher for control than obstructed animals ($p < 0.001$).

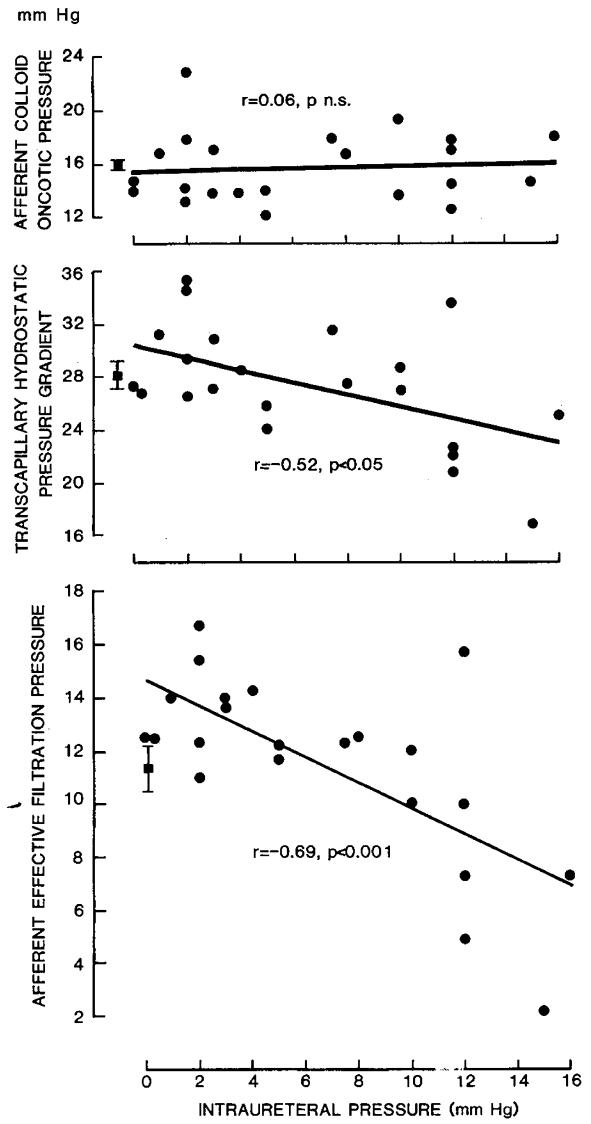

Fig. 5. Pressure gradients affecting glomerular ultrafiltration *versus* intraureteral pressure. *Top panel*: oncotic pressure; $y = 0.03x + 15.6$. *Middle panel*: hydrostatic pressure; $y = -0.46x + 30.4$. *Lower panel*: afferent effective filtration pressure; $y = -0.48x + 14.7$. *Symbols* are the same as in Figure 3.

DISCUSSION

Technical considerations. Whole kidney GFR could not be accurately measured by inulin clearance in animals with CPUO because of the significant dead space created by a dilated renal pelvis and ureter proximal to the obstruction, as well as possible inulin leakage across obstructed tubules (20). As the proximal tubule was proportionately less dilated by CPUO than distal tubule or collecting system, and as measured $(TF/P)_{in}$ ratio was not altered by CPUO in the present study, superficial SNGFR could be measured in each group by tubular fluid collections. However, these experiments show that by reducing P_{PT}, free flow proximal tubular fluid collection overestimates SNGFR in the developing guinea pig. By maintaining the initial P_{PT} with application of counterpressure during tubular fluid collection, this variable could be controlled.

In the present study, P_{GC} was calculated from P_{SF} rather than directly measured, because of the paucity of surface glomeruli in the guinea pig (5). Measurement of P_{SF} was unaffected by prior tubular fluid collection from the same nephron. However, a recent report suggests that, in the hydropenic adult rat, P_{GC} calculated from P_{SF} may overestimate directly measured P_{GC} (12). Others have not confirmed these findings (15). Furthermore, Kaskel *et al.* (16) have demonstrated a close correlation between P_{GC} calculated from P_{SF} and that measured by direct puncture of glomerular capillaries in guinea pigs 2 h to 10 days old. Arendshorst *et al.* (1) have also shown no difference in P_{GC} measured by the two techniques either in control hydropenic rats or in animals with markedly elevated P_{PT} as a result of temporary renal ischemia. Wright (23) maintains that P_{SF} is a reliable indicator of P_{GC}, as changes in directly measured P_{GC} during complete unilateral ureteral obstruction in the rat closely parallel changes observed in P_{SF}. Taken together, experimental evidence thus strongly supports the use of P_{SF} for determination of P_{GC} in the developing guinea pig with CPUO.

Effects of intraureteral pressure on SNGFR. While ureteral obstruction at birth resulted in intraureteral pressure varying from normal to significantly elevated measurements at 3 wk of age, all animals had ureteral dilatation proportional to P_U. Progressive ureteral dilatation following ureteral obstruction in early development is due to hyperplasia of leiomyocytes (8) and deposition of connective tissue after 2 wk of CPUO (9). A significant correlation of P_U with kidney weight and an inverse correlation with body weight implies that several morphometric correlates of CPUO in the neonate are directly or indirectly related to continued intraureteral pressure elevation. Dependence of intratubular pressure on urine flow is well established in the normal kidney (11) and would be accentuated by the increased ureteral resistance in guinea pigs with CPUO. As hematocrit and plasma total protein concentration were maintained constant in the present study, intravascular volume presumably remained unchanged during the experiment, and measured P_U reflects that present at normal urine flow rates. The close negative correlation between P_U and superficial SNGFR indicates that factors leading to P_U elevation are also important determinants of ultrafiltration in neonatal CPUO. As maturation of superficial nephrons takes place most rapidly in the guinea pig between 2 and 4 wk of age (21), it is possible that functional development is more easily disrupted in outer than inner glomeruli when CPUO is present at this time. The observed decrease in superficial SNGFR also parallels a shift in renal blood flow distribution from outer to inner cortex with severe CPUO in uninephrectomized guinea pigs of similar age (6).

A feature which distinguished kidneys of animals with severe CPUO from those with mild obstruction and controls was the marked heterogeneity of tubular fluid flow rate measured by distal transit time. Rather than forming a graded continuum, however, there appear to be two distinct populations of nephrons in severe CPUO: one with normal and another with prolonged transit time. Increased heterogeneity of SNGFR and nonfiltering nephrons have also been observed following unilateral complete ureteral obstruction (7), or unilateral CPUO (22). As the number of glomeruli perfused per kidney does not change with severity of CPUO in uninephrectomized guinea pigs (6), it is unlikely that heterogeneous nephron function is directly due to hemodynamic factors.

Effects of intraureteral pressure on glomerular dynamics. Arterial blood pressure and P_{GC} were unaffected by CPUO and cannot be responsible for diminished SNGFR. As both P_{DT} and P_{PT} increased with elevation of intraureteral pressure due to CPUO, pressure in Bowman's space presumably rose proportionately.

Peritubular capillary hydrostatic pressure also rose with increasing P_U. This may have been due to vascular compression by dilated tubules (10,14) or to increased postglomerular blood flow resulting from lower filtration fraction (6). Animals with mild CPUO presumably failed to demonstrate a rise in P_{PT} and P_{DT} because elevation of P_U in the normal animal does not affect tubular pressure until preexisting hydrostatic pressure is exceeded (10). As elevation of P_U in kidneys with collapsed tubules does not result in elevated P_{PT} (10), hydrostatic pressure is not simply transmitted directly back to the glomerulus, but is altered by

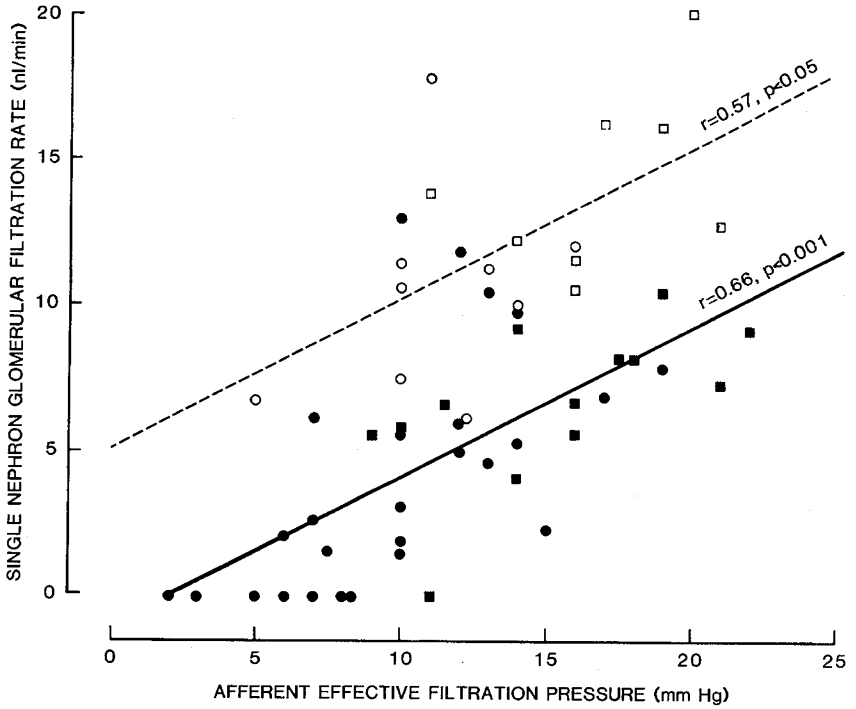

Fig. 6. Single nephron glomerular filtration rate *versus* afferent effective filtration pressure for individual nephrons. *Closed symbols* represent measurements in animals with CPUO with regression ($y = 0.51x - 1.00$) given as *solid line. Open symbols* represent measurements in control uninephretomized animals with regression ($y = 0.52x + 5.07$) depicted by *broken line. Circles* represent measurements of SNGFR made during application of counterpressure to maintain initial intratubular pressure while *squares* represent measurements by free flow collection of tubular fluid.

changes in resistance and permeability of each tubular segment. As P_{PT} exceeds P_{DT} in control guinea pigs as well as those with CPUO, the loop of Henle must contribute effective resistance to tubular fluid flow irrespective of the degree of ureteral obstruction. Therefore, just as P_U was found to vary widely in animals with originally uniform ureteral obstruction, there may be differences in individual nephron resistance due to variable distortion of Henle's loops despite the fact that all nephrons drain into a pelvis with uniform hydrostatic pressure.

In considering pressure gradients determining ultrafiltration, oncotic and hydrostatic, only the latter were affected by increasing P_U. The resulting decrease in EFP_A in severe compared to mild CPUO suggests that transglomerular pressure gradients contribute significantly to reduced SNGFR in this group. However, when compared to control animals, EFP_A was not significantly lower following severe CPUO although SNGFR was reduced by 70%. In both CPUO and control groups, SNGFR increased by 1 nl/min for each 2 mm Hg increment in EFP_A although a constant difference in SNGFR of 6 nl/min at any EFP_A points to the influence of the remaining determinants of ultrafiltration: glomerular plasma flow and ultrafiltration coefficient. Results of hemodynamic studies show that renal blood flow tended to be lower in guinea pigs with severe CPUO than in uninephretomized controls, but differences were not signficant (6). For severe CPUO, even when a 6% redistribution of blood flow from outer to inner cortical levels is taken into account (6), superficial nephron perfusion would be no more than 27% lower than in controls. The only explanation for severely reduced SNGFR in this group is therefore a decrease in ultrafiltration coefficient of at least 33%. For animals with mild CPUO, in which superficial SNGFR was not different from that in controls, the presumed decrease in ultrafiltration coefficient was counterbalanced by a tendency to higher EFP_A. Similar conclusions were reached in a study of mild CPUO in the adult rat, in which SNGFR remained normal despite marked reduction in ultrafiltration coefficient (13). In contrast to the neonatal guinea pig, P_{GC} was elevated by CPUO in this study (13).

In summary, CPUO in the uninephrectomized newborn guinea pig results in complex alterations in glomerular dynamics which are related to the severity of elevation in P_U. Rather than hydrostatic pressure simply being transmitted back to the glomerulus with SNGFR being dependent on net EFP_A, the effects of increased P_U on SNGFR appear to be mediated via subtle hemodynamic changes and reduction in ultrafiltration coefficient. Whether ultrafiltration coefficient is altered primarily by changes in filtration surface area or in glomerular permeability cannot be determined from these data. It is likely that locally produced vasoactive compounds such as angiotensin and prostaglandins are responsible for changes in ultrafiltration coefficient as well as in resistance of the renal microvasculature (13). The interrelationships of renal hormones in the adult kidney are poorly understood, and are even less clear in the developing kidney in which nephron heterogeneity and rapidly changing glomerular dynamics also modulate glomerular filtration rate. Elucidation of mechanisms responsible for the observed effects of CPUO in the neonate will most likely depend on further advances in renal endocrinology.

Acknowledgments. The assistance of Dr. Donald Kaiser in performance of statistical analysis is gratefully acknowledged. Secretarial assistance was provided by Ms. Jean De Piro.

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0031-3998/84/1812-1277$02.00/0
PEDIATRIC RESEARCH
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Vol. 18, No. 12, 1984
Printed in U.S.A.

Inotropic Effects of Prostaglandin D_2 and E_1 on the Newborn Rabbit Heart

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ABSTRACT. This study determines the inotropic effects of prostaglandin D_2 (PGD_2) and prostaglandin E_1 (PGE_1) in the isolated, arterial perfused newborn (NB) and adult (A) rabbit heart.

Significant positive inotropism of PGD_2 was observed at all concentrations studied (1×10^{-17} to 1×10^{-7} M) in the two age groups; the effect in the NB was significantly greater ($p < 0.05$) than that in the A at PGD_2 concentrations higher than 1×10^{-17} M. Significant positive inotropism of PGE_1 was observed at PGE_1 concentrations higher than 1×10^{-8} M in the NB, and only at 1×10^{-6} M in the A.

In the NB, the relaxation parameters [½RT and the ratio of $+dT/dt$ (max) to $-dT/dt$ (max)] decreased to 80% of control after PGE_1 infusion, but not after PGD_2 infusion. In contrast, relaxation parameters in the A were not different from control.

Propranolol (1×10^{-6} M) did not alter the positive inotropic action of PGD_2 and PGE_1 in the NB. These data indicate that: 1) the positive inotropic effects of PGD_2 and PGE_1 in NB are greater than that in the A, 2) PGE_1 and not PGD_2, enhances myocardial relaxation only in the NB, 3) the contractile effects of PGD_2 and PGE_1 are not mediated by β-receptors. (*Pediatr Res* 18:1277–1281, 1984)

September 29, 1983; accepted April 13, 1984.

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This work was supported by Research Grants HL-24148 and HL-25476 from The National Heart, Blood, and Lung Institute, and Research Grant 744G1-1 and Group Investigator Award 5061G9 from the American Heart Association, Greater Los Angeles Affiliate.

Abbreviations

PGE_1, prostaglandin E_1
PGD_2, prostaglandin D_2
DT, developed tension
RT, resting tension
$+dT/dt$ (max), maximal rate of tension development
$-dT/dt$ (max), maximal rate of relaxation
½RT, half-relaxation time

PGE_1 has been used to maintain the patency of the ductus arteriosus in the newborn with ductus-dependent congenital heart disease (9). Recent studies in fetal and newborn lambs (5, 32) showed that PGD_2 decreased the pulmonary arteriolar resistance and suggested that PGD_2 may be used to treat newborns with persistent pulmonary hypertension (5, 32). However, little is known about the inotropic effects of prostaglandins in the newborn. Previous reports of the influence of PGs on myocardial contractility in the adult are inconsistent (18, 19). These contradictory results may be due to heart rate variability (4, 34), extracellular Ca^{2+} concentration [Ca^{2+}] (20), species (4, 19), and the experimental preparation (19, 34).

This study was designed to determine the action of PGE_1 and