# Glomerular and Tubular Adaptive Responses to Acute Nephron Loss in the Rat

## Effect of Prostaglandin Synthesis Inhibition

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## Abstract

**These studies, using in vivo micropuncture techniques in the Munich-Wistar rat, document the magnitude of changes in glomerular and tubular function and structure 24 h after ~ 75% nephron loss (Nx) and compared these results with those obtained in sham-operated rats. The contribution of either nephron hypertrophy or renal prostaglandin to these adjustments in nephron function was also explored. After acute Nx, single nephron GFR (SNGFR) was increased, on average by ~ 30%, due primarily to glomerular hyperperfusion and hypertension. The ~ 45% reduction in preglomerular and the constancy in postglomerular vascular resistances was entirely responsible for these adaptations. Although increases in fluid reabsorption in proximal convoluted tubules correlated closely with increases in SNGFR, the fractional fluid reabsorption between late proximal and early distal tubular segments was depressed. Nephron hypertrophy could not be substantiated based on either measurements of protein content in renal tissue homogenates or morphometric analysis of proximal convoluted tubules. However, acute Nx was associated with increased urinary excretory rates per functional nephron for 6-keto-$PGF_{1\alpha}$ and $TXB_2$. Prostaglandin synthesis inhibition did not affect function in control nephrons, but this maneuver was associated with normalization of glomerular and tubular function in remnant nephrons. The results suggest that enhanced synthesis of cyclooxygenase-dependent products is one of the earliest responses to Nx, and even before hypertrophy the pathophysiologic effects of prostaglandin may be important contributors to the adaptations in remnant nephron function. (*J. Clin. Invest.* 1990. 85:1761–1769.) kidney micropuncture study • glomerular hemodynamics • renal tubular fluid reabsorption • renal hypertrophy • cyclooxygenase inhibition**

## Introduction

Loss of renal mass and excretory function produced experimentally by renal ablation in the rat (Nx) results in increased function and structural hypertrophy of the remnant nephrons and ultimately in progressive glomerulosclerosis and end-stage renal disease (1–5). Although these chronic compensatory adjustments have been regarded as obligatory for the long-term preservation of a near-normal biological milieu, recent investigations have proposed that these compensatory adjustments in normal or minimally diseased remnant nephrons are central to the progressive nature of renal disease (6, 7). Further insight into the mechanism responsible for the progressive nature of renal disease could be achieved with studies that examine the temporal development of functional and structural changes after Nx.

Free-flow micropuncture studies in rat remnant kidneys have shown, in the chronic state, that in the surviving remnant nephrons glomerular hyperfiltration is proportional to the extent of the initial reduction in renal mass (8) and maintained by significant increases in single nephron plasma flow (SNPF) and glomerular capillary hydrostatic pressure difference ($\Delta P$) (4). Chronically, these glomerular hemodynamic alterations are the direct consequence of a proportionally greater vasodilation in afferent than in efferent arterioles (4, 9, 10). Although these pathophysiologic adaptations have been well characterized in the chronic state, the nature of the stimuli responsible for, and the relative contribution of functional (i.e., humoral–hormonal) and structural (i.e., hypertrophy) changes in this hyperfunctioning state have only recently begun to be elucidated (10, 11). More important, there is a significant gap in our knowledge of the specific mechanisms responsible for the early adjustments in glomerular and tubular function associated with Nx, and there is conflicting evidence as to whether functional or structural changes are the first to be triggered (12, 13). Presumably, these adjustments form the basis for the chronic adaptive changes in remnant nephrons.

These studies were therefore designed to examine the extent to which changes in single nephron GFR (SNGFR), glomerular hemodynamics, segmental tubular fluid reabsorption, and Starling forces for peritubular capillary fluid uptake occur 24 h after Nx. Conventional measurements of renal tissue DNA, RNA, and protein concentrations, as well as morphometric studies in proximal convoluted tubules, were performed to probe the role of structural hypertrophy in the adaptive changes of remnant nephrons. In the current investigation, increases in both glomerular and tubular function after acute Nx were demonstrated. This hyperfunctioning state could not be explained by coincident structural hypertrophy, but was associated with augmented urinary excretory rates per nephron for vasodilatory (i.e., $PGI_2$) and vasoconstrictor (i.e., $TXA_2$) prostaglandin. In light of these findings, the role of prostaglandin in mediating the increase in SNGFR and its determinants, as well as the altered tubular segmental fluid reabsorption, was investigated in another group of rats during the acute inhibition of prostaglandin synthesis. The results from these studies suggest that a vasodilatory prostaglandin, possibly $PGI_2$, whose activity is increased in response to acute Nx, contributes to the regulation of solute and water balance

Portions of these studies were presented at the 21st Annual Meeting of the American Society of Nephrology, Washington, DC, 1988, and published in abstract form (1989. *Kidney Int.* 35:468a, 500a).

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by increasing SNGFR and thus augmenting the excretion of fluid by each remaining nephron.

## Glossary

| | |
|---|---|
| $\Delta P$ | glomerular capillary hydrostatic pressure difference |
| $\pi_A$ | afferent oncotic pressure |
| $\pi_E$ | efferent oncotic pressure |
| $\pi_i$ | interstitial oncotic pressure |
| ALR | absolute pars recta and loop of Henle reabsorption |
| APR | absolute proximal tubule reabsorption |
| $C_A$ | systemic serum protein concentration |
| $C_E$ | efferent serum protein concentration |
| $C_i$ | interstitial protein content |
| $FE_{Na}$ | fractional excretion of sodium |
| FF | filtration fraction |
| $FR_{dist}$ | early distal tubule fractional reabsorption |
| $FR_{prox}$ | late proximal tubule fractional reabsorption |
| Hct | hematocrit |
| LpA | glomerular ultrafiltration coefficient |
| LpAr | peritubular capillary reabsorption coefficient |
| MAP | mean arterial pressure |
| Nx | nephron loss |
| $P_{BS}$ | Bowman's space hydrostatic pressure |
| $P_C$ | small peritubular capillary hydrostatic pressure |
| $P_E$ | efferent arteriolar hydrostatic pressure |
| $P_{EF}$ | mean effective filtration pressure |
| $P_{ER}$ | mean effective reabsorptive pressure |
| $P_G$ | glomerular capillary hydrostatic pressure |
| PGs Inhib | the experimental period during which prostaglandin synthesis was acutely inhibited |
| $P_i$ | interstitial hydrostatic pressure |
| $P_T$ | proximal tubule hydrostatic pressure |
| $R_A$ | afferent arteriolar resistance |
| RBF | renal blood flow |
| $R_E$ | efferent arteriolar resistance |
| RPF | renal plasma flow |
| Sh | sham operation |
| SNBF | single nephron blood flow |
| SNFF | single nephron filtration fraction |
| SNPF | single nephron plasma flow |
| $SNPF_E$ | efferent single nephron plasma flow |
| $U_{Na}V$ | urinary sodium excretion |
| V | urinary blood flow |
| $V_{Fdist}$ | early distal tubule flow rate |
| $V_{Fprox}$ | late proximal tubule flow rate |

## Methods

*Experimental animals.* Five groups of adult male Munich-Wistar rats (Simonsen Laboratories, Inc., Gilroy, CA), weighing 205–275 g at the time of the study, were used in this investigation. All animals were given free access to tap water and fed a standard pellet diet (Wayne Lab-Blox; Golden K. Feed and Seed, Longmont, CO) containing ~ 22% protein by weight.

*Surgical preparation for micropuncture studies.* Rats were anesthetized with Inactin (100 mg · kg body $wt^{-1}$ i.p.; Byk-Gulden-Lomberg, Konstanz, FRG) and placed on a micropuncture table with a servo-controlled heating unit (Yellow Springs Instrument Co., Yellow Springs, OH). Body temperature was maintained at 36.5–37.5°C. In each rat, a tracheostomy tube (PE-240) was inserted to insure adequate ventilation. The left femoral artery and the left external jugular vein were cannulated to permit the withdrawal of blood samples and continuous monitoring of mean arterial blood pressure (MAP), and for the infusion of [$^3$H]inulin, plasma, and indomethacin. MAP was monitored continuously throughout the studies with an electronic pressure transducer, model P23 Db, and recorded on an amplifier chart recorder, model 8000S (Gould Inc., Oxnard, CA). Indwelling catheters (PE-50) were also inserted into the left ureter and bladder for timed urine collections. The left experimental kidney was surgically exposed via a flank incision and prepared according to standard micropuncture protocols (14). To compensate for the loss of plasma associated with the surgical preparation required for a micropuncture study, all rats received a continuous intravenous infusion of homologous rat plasma at 1.0–1.5 ml · 100 g body $wt^{-1} \cdot h^{-1}$ for 60 min, followed by a maintenance infusion of 0.15–0.2 ml · 100 g body $wt^{-1} \cdot h^{-1}$ for the duration of each experiment (10). Each sham-operated or nephrectomized rat also received an intravenous infusion of isotonic NaCl-$NaHCO_3$ (0.5 or 0.25% body wt · $h^{-1}$, respectively). 60 min before the micropuncture measurements [$^3$H]inulin (ICN Pharmaceuticals, Irvine, CA) was added to the isotonic NaCl-$NaHCO_3$ solution to provide 150 $\mu$Ci · $h^{-1}$ throughout the study as a marker of glomerular ultrafiltration.

*Micropuncture measurements of the determinants of glomerular ultrafiltration and peritubular capillary fluid uptake.* Hydrostatic pressures were measured by a servo-nulling pressure sensor (Instrumentation for Physiology and Medicine, San Diego, CA) in surface glomerular capillaries ($P_G$), Bowman's space ($P_{BS}$), proximal tubules ($P_T$), efferent arterioles (star vessels, $P_E$), small peritubular capillaries ($P_C$), and cortical interstitium ($P_i$) (10). Hydrostatic output from the servo-null system was monitored with a second electronic pressure transducer, model P23 Gb, and recorded on a second channel of the amplifier chart recorder (Gould Inc.). Exactly timed (2–3 min) tubular fluid samples were collected from paired surface late proximal tubular convolutions and early distal tubular segments of at least three nephrons for determination of [$^3$H]inulin radioactivity and calculation of SNGFR, tubular fluid flow rate, and reabsorption. These tubular segments were identified by the intratubular injection of nanoliter volumes of isotonic NaCl-$NaHCO_3$ lightly stained with FD & C green (Allied Chemical Co., Morristown, NJ) (14). Simultaneously with these tubular fluid collections, two blood specimens from the femoral artery catheter were collected for determination of arterial hematocrit (Hct), plasma [$^3$H]inulin radioactivity, and systemic serum protein concentration ($C_A$). Efferent arteriolar blood samples were collected from at least three star vessels for determination of postglomerular serum protein concentrations ($C_E$) (10). Lymph samples were obtained (20-$\mu$m tip diameter pipettes) from hilar lymph vessels for measurement of protein content ($C_i$). Urine from the right and left experimental kidneys was collected for determination of flow rate (V) and [$^3$H]-inulin radioactivity, prostaglandin and sodium concentrations, and calculation of whole kidney GFR, urinary prostaglandin excretion, urinary sodium excretion ($U_{Na}V$), and fractional excretion of sodium ($FE_{Na}$). Urine samples were stored at −20°C until assayed for prostaglandin concentration. At the end of the micropuncture studies, renal vein blood samples were also obtained (via siliconized 100-$\mu$m tip diameter pipettes) to determine renal plasma flow (RPF) and renal blood flow (RBF) (9).

*Experimental groups.* For these studies, rats underwent either sham operation (Sh) or ~ 75% Nx by removal of the right kidney and infarction of approximately half of the left kidney by ligation of two to three branches of the renal artery (10). During the surgical procedure, rats were anesthetized with methohexital sodium (50 mg · kg body $wt^{-1}$ i.p.; Brevital® sodium; Eli Lilly and Co., Indianapolis, IN) and then returned to their individual cages after recovering from anesthesia. On the following day, unpaired micropuncture measurements were performed in sham-operated rats (group 1dSh, $n$ = 8) and rats subjected to Nx (group 1dNx, $n$ = 8). At the completion of the micropuncture studies animals were killed, their left experimental kidneys

were removed, a portion was snap-frozen in liquid nitrogen and stored at −70°C until assayed for DNA, RNA, and protein content, and the remaining tissue was processed for morphometric assessment of proximal convoluted tubule diameter and cell height. In addition, in a separate group of rats with Nx, morphometric evaluation was performed 2 wk after surgery (group 2wkNx, $n = 6$).

The second micropuncture protocol consisted of paired investigations at 1 d after either sham operation (group 1dSh-ID, $n = 7$) or Nx (group 1dNx-ID, $n = 9$), in which physiologic measurements obtained during vehicle infusion ($Na_2CO_3$) in the initial control period (vehicle) were repeated in the experimental period during which prostaglandin synthesis was acutely inhibited (PGs Inhib). Prostaglandin synthesis inhibition was accomplished by the systemic infusion of indomethacin (5 mg · kg body $wt^{-1}$ i.v., bolus; Sigma Chemical Co., St. Louis, MO) (15). The infusion of this test substance was begun 45 min before the experimental period.

*Analytical.* Total volume of each late proximal or early distal tubular collection was determined as described previously (14). [$^3$H]Inulin radioactivity in plasma, tubular fluid, and urinary samples was measured in a model 4000 Minaxi Tri-Carb scintillation counter (Packard Instrument Co. Inc., Downer's Grove, IL). Protein concentrations in systemic, efferent arteriolar, and lymph samples were analyzed by a microadaptation of the Lowry protein method (16, 17). DNA, RNA, and total protein concentrations in kidney tissue homogenates were measured in triplicate by a colorimetric reaction with diphenylamine (18), ultraviolet spectrophotometric absorption (19), and the Coomassie brilliant blue method (20), respectively. For the serum, lymph, and renal tissue protein measurements, rat serum was used for the standards. Urinary prostaglandin was quantitated by enzyme immunoassay as previously described (21, 22). The assay procedures and sensitivity and specificity of the antisera used have been described elsewhere (22). $TXA_2$ was measured as its stable metabolite $TXB_2$, whereas $PGI_2$ was assessed as its metabolite 6-keto-$PGF_{1\alpha}$. Sodium concentration in urinary samples was determined by flame photometry (Instrumentation Laboratory, Inc., Lexington, MA).

*Morphometric studies.* The kidneys from rats of groups 1dSh, 1dNx, and 2wkNx were immersion-fixed in 10% buffered formalin and embedded in glycol methacrylate, and 1-μm-thick sections representing ~ 1 × 0.5 cm area were stained by a standard periodic acid–Schiff technique. Morphometric evaluation was done using a Zidas image analyzer (Zeiss Interactive Digital Analysis System; Carl Zeiss Inc., Oberkochen, FRG) with the method previously described (9). In each experiment the cell height and tubular diameter in 20 consecutive proximal convoluted tubules encountered along a line through the mid-cortex were determined.

*Calculations.* Oncotic pressures in afferent ($\pi_A$) and efferent ($\pi_E$) arteriolar blood samples and renal interstitium ($\pi_i$) were estimated from systemic and efferent arteriolar serum and renal lymph protein concentrations, respectively, as described elsewhere (23). GFR, FF, RPF, RBF, $U_{Na}V$, and $FE_{Na}$ were estimated using standard equations. SNGFR, its determinants, and preglomerular ($R_A$) and postglomerular ($R_E$) vascular resistances were calculated as previously described (14). Specific values for the glomerular ultrafiltration coefficient (LpA) could be determined for each group of rats because a condition of filtration pressure disequilibrium (i.e., $\Delta P > \pi_E$) was demonstrated in each rat. Absolute (APR) and fractional ($FR_{prox}$) tubular fluid reabsorption in the proximal tubule, absolute fluid reabsorption in the pars recta and loop of Henle (late proximal to early distal) (ALR), and fractional tubular fluid reabsorption in the early distal segment ($FR_{dist}$) were computed as described elsewhere (24). The determinants of peritubular capillary fluid uptake from the interstitial space into the peritubular capillary were determined by an iterative procedure as described previously (14).

*Statistical.* All data are expressed as means±SE. Statistical analysis was performed using a statistics software package (Crunch Software Co., San Francisco, CA) and Personal System/2 computer model 50 (IBM Co., Boca Raton, FL). Statistical significance between groups of animals was calculated by unpaired $t$ test; paired $t$ test was used to evaluate changes between periods in paired studies. The difference between means was considered significant for $P < 0.05$.

## Results

### *Effects of acute nephron loss*

*Systemic parameters and glomerular hemodynamics.* GFR, RPF, and RBF were markedly reduced in group 1dNx compared with those in group 1dSh, but FF was not different. V and $U_{Na}V$ were not different between groups; however, $FE_{Na}$ in comparison with group 1dSh increased significantly by 2.5-fold in group 1dNx (Tables I and II).

Although the two groups were similar with respect to MAP, SNGFR in group 1dNx was ~ 30% higher than in group 1dSh. Glomerular hyperfiltration in group 1dNx could be primarily attributed to increments in both SNPF and ΔP. Of importance, glomerular hyperperfusion and hypertension were the direct result of the dissimilar responses of the pre- and postglomerular resistances to acute nephron loss. In group 1dNx, $R_A$ was ~ 45% lower, whereas $R_E$ was not significantly modified compared with group 1dSh.

*Tubular reabsorption and the determinants of peritubular capillary fluid uptake.* With the increment in SNGFR, APR and $V_{Fprox}$ increased proportionally in group 1dNx, and these values were higher than those attained in group 1dSh (Table III). A highly significant correlation was found between SNGFR and APR ($r = 0.8$, $P < 0.0001$), indicating a nearly perfect glomerulotubular balance. Acute nephron loss was associated with reductions in $FR_{dist}$, however ALR was not altered. Therefore, $V_{Fdist}$ was significantly higher in group 1dNx than in group 1dSh. The increase in APR, and thus in peritubular capillary fluid uptake in group 1dNx, ensued without any significant alteration in $\pi_E$. However, as compared with group 1dSh, group 1dNx had higher values for $P_E$ and $P_i$, and lower values for $\pi_i$. These adaptations in the Starling forces produced a significant reduction in the net transperitubular capillary pressure [$P_E - (P_i - \pi_i)$] (11.3±0.8 mmHg in group 1dNx vs. 16.0±1.0 mmHg in group 1dSh, $P < 0.01$), which counters the oncotic reabsorptive pressure, resulting in a higher value for the mean effective reabsorptive pressure ($P_{ER}$)

*Table I. Summary of Hct and Whole Kidney Data in Groups 1dSh and 1dNx Rats*

| Group | Hct | GFR | FF | RPF | RBF | V | $U_{Na}V$ | $FE_{Na}$ |
|---|---|---|---|---|---|---|---|---|
| | *vol%* | *ml/min* | | *ml/min* | *ml/min* | *μl/min* | *μEq/min* | *%* |
| 1dSh ($n = 8$) | 48.3±0.9 | 1.65±0.09 | 0.26±0.01 | 6.6±0.4 | 12.7±1.0 | 15.9±3.8 | 3.3±0.6 | 1.47±0.27 |
| 1dNx ($n = 8$) | 48.5±0.7 | 0.40±0.02* | 0.27±0.02 | 1.6±0.2* | 3.1±0.4* | 15.7±3.0 | 2.2±0.4 | 3.76±0.68* |

See Glossary for definitions of terms. Values are means±SE. *$P < 0.05$, group 1dNx vs. group 1dSh.

*Table II. Summary of Systemic and Glomerular Hemodynamic Results in 1dSh and 1dNx Groups*

| Group | MAP | $P_G$ | $P_{BS}$ | $\Delta P$ | $C_A$ | $C_E$ | $\pi_A$ | $\pi_E$ | SNFF | SNGFR | SNPF | SNBF | $R_A$ | $R_E$ | $P_{EF}$ | $L_pA$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *mmHg* | *mmHg* | *mmHg* | *mmHg* | *g/dl* | *g/dl* | *mmHg* | *mmHg* | | *nl/min* | *nl/min* | *nl/min* | $\times 10^9$ *dyn·s·cm$^{-5}$* | $\times 10^9$ *dyn·s·cm$^{-5}$* | *mmHg* | *nl/s·mmHg* |
| 1dSh ($n$ = 8) | 104±4 | 53.9±0.7 | 14.4±0.7 | 40.2±1.5 | 5.5±0.2 | 7.5±0.2 | 18.1±1.0 | 29.1±1.3 | 0.27±0.02 | 37.5±2.0 | 144.2±15.0 | 279.4±30.5 | 15.4±1.5 | 13.6±1.7 | 16.9±1.1 | 0.048±0.012 |
| 1dNx ($n$ = 8) | 109±4 | 65.8±1.9* | 18.3±0.6* | 47.9±1.3* | 5.8±0.2 | 7.7±0.2 | 20.2±1.1 | 30.2±1.1 | 0.23±0.02 | 49.1±2.0* | 225.3±24.8* | 437.9±48.1* | 8.4±0.9* | 10.4±1.0 | 23.2±1.7* | 0.037±0.003 |

Values are means±SE. *$P < 0.05$, group 1dNx vs. group 1dSh.

*Table III. Summary of Tubular Reabsorption and the Determinants of Peritubular Capillary Fluid Uptake Results in 1dSh and 1dNx Groups*

| Group | SNGFR | $FR_{prox}$ | APR | $V_{Pprox}$ | $FR_{dist}$ | ALR | $V_{Pdist}$ | $SNPF_E$ | $\pi_E$ | $\pi_i$ | $P_T$ | $P_i$ | $P_E$ | $P_C$ | $P_{ER}$ | LpAr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *nl/min* | | *nl/min* | *nl/min* | | *nl/min* | *nl/min* | *nl/min* | *mmHg* | *mmHg* | *mmHg* | *mmHg* | *mmHg* | *mmHg* | *mmHg* | *nl/s·mmHg* |
| 1dSh ($n$ = 8) | 37.5±2.0 | 0.38±0.02 | 14.7±1.0 | 22.8±0.9 | 0.65±0.01 | 9.7±0.6 | 13.0±0.9 | 110.5±13.9 | 29.1±1.3 | 5.5±0.6 | 13.9±0.7 | 5.4±0.3 | 15.9±0.6 | 11.3±0.4 | 12.9±1.4 | 0.020±0.002 |
| 1dNx ($n$ = 8) | 49.1±2.0* | 0.37±0.02 | 18.9±1.7* | 30.1±1.1* | 0.57±0.02* | 10.3±1.1 | 21.1±1.6* | 176.2±23.7* | 30.2±1.1 | 3.4±0.5* | 18.3±0.6* | 10.4±0.5* | 18.3±0.6* | 13.0±0.6* | 19.0±1.1* | 0.017±0.001 |

Values are means±SE. *$P < 0.05$ group 1dNx vs. group 1dSh.

in group 1dNx than in group 1dSh. The mean values for the peritubular capillary reabsorptive coefficient (LpAr) were not different between groups.

*Renal DNA, RNA, and protein content.* Results for DNA, RNA, and protein content in kidney tissue homogenates were normalized for milligrams of viable dry kidney weight because the dry to wet tissue weight ratio was higher in group 1dSh than in group 1dNx (0.180±0.002 vs. 0.169±0.005, $P < 0.05$), indicating a greater $H_2O$ content in remnant kidney tissue than in intact kidney tissue (Table IV). 24 h after Nx, the kidney content of RNA and RNA/DNA ratio (1.38±0.01 in group 1dNx vs. 1.20±0.01 in group 1dSh, $P < 0.01$) were slightly but significantly increased in group 1dNx compared with group 1dSh. No significant differences in DNA, protein content, and protein/DNA ratio (33.3±1.3 in group 1dNx vs. 30.8±1.3 in group 1dSh) were evident between groups.

*Morphometric analysis.* Comparison of 1dNx and 1dSh groups showed no significant differences in proximal convoluted tubular outer diameter or cell height (Fig. 1). To be assured that such changes could be discerned with our technique, we also examined these parameters in rats 2 wk after Nx (group 2wkNx). The mean cell height was not different from 1dSh and 1dNx groups 2 wk after Nx, but the tubular diameter was significantly increased.

*Urinary prostaglandin excretion.* Absolute urinary excretions of 6-keto-$PGF_{1\alpha}$, $PGE_2$, and $TXB_2$ from the left experimental kidney of 1dNx and 1dSh groups were not significantly different (Table V). The urinary excretory rates per functional nephron in both groups of rats for 6-keto-$PGF_{1\alpha}$, $PGE_2$, and $TXB_2$ were also calculated, with nephron number being estimated as the quotient of GFR and SNGFR. When corrected per functional nephron, the absolute urinary excretions of 6-keto-$PGF_{1\alpha}$ and $TXB_2$ were increased significantly by approximately twofold in group 1dNx in comparison with group 1dSh.

### *Effects of acute prostaglandin inhibition in a setting of acute nephron loss*

*Systemic parameters and glomerular hemodynamics.* Mean values in the vehicle period were not different from those in the PGs Inhib period for MAP, Hct (46.5±0.4 vs. 47.8±0.4 vol%), GFR (1.79±0.06 vs. 1.77±0.08 ml/min), and V (12.2±1.4 vs. 11.8±1.2 μl/min) in group 1dSh-ID (Table VI). Acute prostaglandin synthesis inhibition in group 1dSh-ID did not significantly alter the baseline values for SNGFR or its determinants.

Conversely, acute prostaglandin synthesis inhibition in group 1dNx-ID resulted in a significant reduction in both GFR and V (from 0.50±0.07 in vehicle to 0.42±0.07 ml/min in PGs Inhib, $P < 0.001$, and from 15.7±1.6 in vehicle to 6.7±1.4 μl/min in PGs Inhib, $P < 0.005$, respectively). MAP was not different between periods, but Hct values were slightly higher in vehicle than those in PGs Inhib (47.2±0.6 vs. 46.4±0.7 vol%, $P < 0.05$, respectively). As was the case with GFR, SNGFR fell after the acute infusion of indomethacin on average by ~ 25%, due primarily to the concomitant declines in SNPF and ΔP; a pronounced increase in $R_A$ in PGs Inhib compared with vehicle accounted entirely for these changes since $R_E$ remained nearly constant.

*Tubular reabsorption and the determinants of peritubular capillary fluid uptake.* Acute prostaglandin synthesis inhibition in group 1dSh-ID did not induce changes in tubular reab-

*Table IV. Influence of Acute Nx on DNA, RNA, and Protein Content in Kidney Tissue Homogenates*

| Group | DNA | RNA | Protein |
|---|---|---|---|
| | | *μg/mg dry kidney wt* | |
| 1dSh ($n$ = 8) | 15.8±0.6 | 18.8±0.3 | 482.2±13.5 |
| 1dNx ($n$ = 8) | 15.1±0.6 | 20.8±0.8* | 499.0±19.8 |

Values are means±SE. *$P$ < 0.05 group 1dNx vs. group 1dSh.

sorption or in the determinants of peritubular capillary fluid uptake (Table VII).

The fall in filtered load in group 1dNx-ID was accompanied by a significant and proportional reduction in APR. When the results from both groups were combined, there was a significant correlation between APR and SNGFR ($r$ = 0.6, $P$ < 0.01). This reabsorptive adaptation was attended by significant decreases in two of the Starling forces for peritubular capillary fluid uptake, namely, $P_E$ and $P_i$. The observed decline in the intratubular load of glomerular filtrate in PGs Inhib, coupled with near constancy in $FR_{prox}$, brought about a significant reduction in $V_{Fprox}$. Mean values for $FR_{dist}$ were numerically higher in PGs Inhib compared with those in vehicle, but these changes did not achieve statistical significance. Although ALR was not different between periods, $V_{Fdist}$ was significantly reduced.

*Urinary prostaglandin excretion.* After pretreatment with indomethacin, the baseline values for the absolute excretory rates of 6-keto-$PGF_{1\alpha}$, $PGE_2$, and $TXB_2$ were similarly reduced in both 1dNx-ID (from 170.5±31.4 to 23.7±4.3 pg/min, $P$ < 0.001; from 114.4±39.0 to 8.7±1.1 pg/min, $P$ < 0.005; and from 20.7±2.8 to 6.1±0.3 pg/min, $P$ < 0.001, respectively) and 1dSh-ID groups (from 111.5±16.4 to 22.7±6.5 pg/min, $P$ < 0.0025; from 117.6±48.4 to 11.2±1.6 pg/min, $P$ < 0.005; and from 23.3±5.6 to 9.5±2.8 pg/min, $P$ < 0.01, respectively).

## Discussion

A hyperfunctioning state of surviving remnant nephrons characterizes the chronic response to reduction in renal mass and excretory function of mature mammals (4, 5). There is, however, a paucity of information as to the timing, magnitude, and sequence of early adjustments in glomerular and tubular function that ensue shortly after acute Nx, and which precede and therefore lead to the chronic hyperfiltering state. Specifically, whether such early changes are the result of hormonal–humoral actions and/or hypertrophy remains unclear. These studies quantitate the magnitude and directional responses of glomeruli and tubules 24 h after Nx and examine hormonal and structural-dependent mechanisms by which nephron function in the remnant kidney may be regulated. The results from our in vivo micropuncture studies provide evidence that a hyperfunctioning response can be observed in remnant nephrons 24 h after Nx; this response is not dependent on established hypertrophy but depends on enhanced production of vasodilatory prostaglandin.

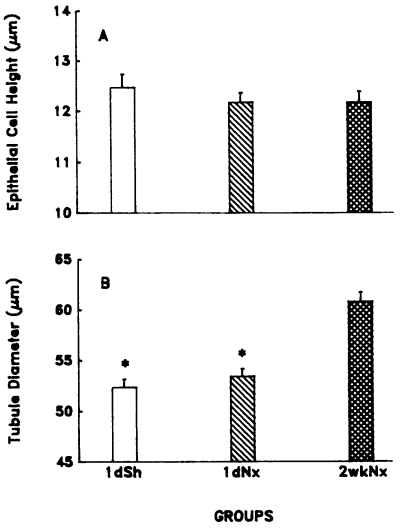


*Figure 1.* Effect of nephron loss on epithelial cell height (*A*) and tubular diameter (*B*) of surface proximal convoluted tubules. *$P$ < 0.05 vs. 2wkNx group.

Although there has been controversy as to whether the nephrons of the remnant kidney possess the capacity to acutely augment GFR in response to a significant loss of functional renal mass, recent studies in volume replete animals have demonstrated that such kidneys do have a striking capacity to compensate, within 24 h of the loss of renal mass and excretory function, by increasing GFR (25). This increment was ascribed to an increase in RPF (25), a consequence of altered vascular resistances, but resistance changes were not addressed in that study. The present data obtained in free-flow micropuncture studies confirm that acute Nx results in a hyperfiltering state. In analogy with what is known about the mechanisms that sustain glomerular hyperfiltration in chronic remnant nephrons (4, 10), the present investigation shows that acute Nx also results in glomerular hyperfiltration via increases in both SNPF and ΔP. Although several hemodynamic mechanisms could potentially explain these acute responses to Nx, marked dilation of the afferent arteriole and maintenance of efferent arteriolar tone was the mechanism that accounted entirely for the observed glomerular hyperperfusion and hypertension in remnant nephrons, since MAP was not modified by acute Nx. Thus, the marked reduction in $R_A$ acts primarily to increase SNPF, which, concurrently with the constancy in

*Table V. Rate of Urinary Prostaglandin Excretion in Groups 1dSh and 1dNx Rats*

| Group | 6-keto-$PGF_{1\alpha}$ | | $PGE_2$ | | $TXB_2$ | |
|---|---|---|---|---|---|---|
| | *pg/min* | *$\times 10^{-3}$ pg·nephron$^{-1}$·min$^{-1}$* | *pg/min* | *$\times 10^{-3}$ pg·nephron$^{-1}$·min$^{-1}$* | *pg/min* | *$\times 10^{-3}$ pg·nephron$^{-1}$·min$^{-1}$* |
| 1dSh ($n$ = 8) | 149.0±15.0 | 7.2±0.8 | 47.4±11.4 | 2.2±0.5 | 13.7±1.8 | 0.6±0.1 |
| 1dNx ($n$ = 8) | 122.2±22.0 | 14.6±2.4* | 30.0±8.9 | 3.6±0.9 | 12.6±2.1 | 1.6±0.6* |

Values are means±SE. *$P$ < 0.05 group 1dNx vs. group 1dSh.

*Table VI. Summary of Systemic and Glomerular Hemodynamic Results in 1dSh-ID and 1dNx-ID Groups*

| Group | MAP | $P_G$ | $P_{BS}$ | $\Delta P$ | $C_A$ | $C_E$ | $\pi_A$ | $\pi_E$ | SNFF | SNGFR | SNPF | SNBF | $R_A$ | $R_E$ | $P_{EF}$ | $L_pA$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *mmHg* | *mmHg* | *mmHg* | *mmHg* | *g/dl* | *g/dl* | *mmHg* | *mmHg* | | *nl/min* | *nl/min* | *nl/min* | *$\times 10^9$ dyn·s·cm$^{-5}$* | *$\times 10^9$ dyn·s·cm$^{-5}$* | *mmHg* | *nl/s·mmHg* |
| 1dSh-ID ($n$ = 7) | | | | | | | | | | | | | | | | |
| Vehicle | 103±3 | 50.8±1.0 | 12.7±0.6 | 38.1±0.5 | 5.8±0.1 | 7.7±0.1 | 19.7±0.7 | 30.2±0.6 | 0.24±0.02 | 42.5±1.0 | 187.3±18.2 | 351.8±34.4 | 12.5±1.1 | 9.8±1.0 | 13.5±0.7 | 0.053±0.003 |
| PGs Inhib | 104±3 | 48.9±0.9 | 12.4±0.4 | 36.6±0.3 | 5.8±0.1 | 7.6±0.1 | 19.4±0.6 | 29.5±0.5 | 0.24±0.02 | 41.7±1.0 | 180.2±15.3 | 346.3±30.7 | 13.2±1.2 | 9.4±0.8 | 12.1±0.4 | 0.059±0.002 |
| 1dNx-ID ($n$ = 9) | | | | | | | | | | | | | | | | |
| Vehicle | 110±3 | 66.2±0.6* | 17.3±0.7* | 49.0±1.0* | 5.9±0.1 | 7.5±0.1 | 20.1±0.3 | 28.8±0.7 | 0.21±0.02 | 51.1±2.3* | 253.2±16.6* | 479.5±31.1* | 7.5±0.6* | 9.3±0.8 | 24.9±1.1* | 0.035±0.012 |
| PGs Inhib | 109±3 | 50.8±1.1‡ | 12.1±0.3‡ | 38.7±1.3‡ | 5.8±0.1 | 7.4±0.2 | 20.0±0.5 | 28.5±1.1 | 0.21±0.02 | 38.6±3.2‡ | 181.8±9.7‡ | 339.0±16.9‡ | 13.9±0.6‡ | 10.1±0.8 | 14.7±1.7‡ | 0.041±0.005 |

Values are means±SE. *$P < 0.05$ group 1dNx-ID vs. group 1dSh-ID. ‡$P < 0.05$ vehicle vs. PGs Inhib.

*Table VII. Summary of Tubular Reabsorption and the Determinants of Peritubular Capillary Fluid Uptake Results in 1dSh-ID and 1dNx-ID Groups*

| Group | SNGFR | $FR_{prox}$ | APR | $V_{Fprox}$ | $FR_{dist}$ | ALR | $V_{Fdist}$ | $SNPF_E$ | $\pi_E$ | $P_T$ | $P_i$ | $P_E$ | $P_C$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *nl/min* | | *nl/min* | *nl/min* | | *nl/min* | *nl/min* | *nl/min* | *mmHg* | *mmHg* | *mmHg* | *mmHg* | *mmHg* |
| 1dSh-ID ($n$ = 7) | | | | | | | | | | | | | |
| Vehicle | 42.5±1.0 | 0.33±0.02 | 14.1±1.4 | 28.3±1.4 | 0.67±0.02 | 15.6±0.8 | 13.0±0.9 | 144.8±18.1 | 30.2±0.6 | 12.9±0.7 | 5.2±0.2 | 14.8±0.8 | 10.5±0.7 |
| PGs Inhib | 41.7±1.0 | 0.33±0.03 | 13.8±1.4 | 27.8±1.4 | 0.68±0.02 | 14.5±1.0 | 13.4±1.6 | 138.5±15.3 | 29.5±0.5 | 12.3±0.5 | 4.9±0.2 | 14.7±0.7 | 10.4±0.4 |
| 1dNx-ID ($n$ = 9) | | | | | | | | | | | | | |
| Vehicle | 51.1±2.3* | 0.34±0.03 | 17.8±1.0* | 34.8±2.8* | 0.57±0.02* | 12.5±1.2 | 22.3±1.5* | 202.0±15.9* | 28.8±0.7 | 17.6±0.5* | 8.8±0.3* | 18.1±0.6* | 13.5±0.5* |
| PGs Inhib | 38.6±3.2‡ | 0.32±0.04 | 11.9±1.8‡ | 25.4±2.1‡ | 0.62±0.03 | 10.9±1.3 | 14.6±1.4‡ | 143.2±8.6‡ | 28.5±1.1 | 12.1±0.5‡ | 5.8±0.2‡ | 13.4±0.6‡ | 9.6±0.5‡ |

Values are means±SE. *$P < 0.05$ group 1dNx-ID vs. group 1dSh-ID. ‡$P < 0.05$ vehicle vs. PGs Inhib.

$R_E$, accounts for the glomerular hypertension. A similar dissociation in the local adjustments of the renal microcirculation of remnant kidneys has been observed in the chronic state (4, 10). In the aggregate, our observations indicate that the adjustments in glomerular hemodynamics in the acute state of nephron loss are qualitatively analogous, although of lesser magnitude, to those that have been previously documented in the chronic state (4, 10).

An early event associated with increased filtration rates in the remnant nephrons, adaptation that augments the flow rate of tubular fluid through the convoluted proximal tubule, was increased APR. This documented ability of the proximal tubule segments to adjust their transepithelial fluid transport in direct proportion to variations in SNGFR supports the contention (25) that glomerulotubular balance is closely maintained in remnant nephrons. Although in general the mechanisms governing glomerulotubular balance remain debatable, based on considerable investigative efforts it appears that peritubular (i.e., Starling forces) and luminal (i.e., intratubular volume flow and solute load) processes, which are in themselves usually linked to the filtered load, exert controlling influences on the maintenance of glomerulotubular balance (26, 27). Through the analysis of the relationship between APR and the reabsorptive determinants operating in the peritubular capillary environment of remnant nephrons, it is evident that LpAr could not contribute to increases in peritubular capillary fluid uptake. Rather, an increase of the pressure gradient across the peritubular capillary wall promoted the movement of fluid from the interstitial compartment to the peritubular capillary network. Of the various Starling forces determining the value of $P_{ER}$, the increase in $P_i$ and the decrease in $\pi_i$ played major roles. Because the described micropuncture measurements were determined in a steady-state condition, it was not feasible to establish with certainty whether the changes in these Starling forces are causal in effecting increases in APR.

In these studies we also examined the effect of acute Nx on fluid reabsorption between the late proximal and early distal tubular segments. ALR was not different between groups even though the rate of fluid delivered to the segments beyond the late proximal puncture site (i.e., primarily loops of Henle) was significantly elevated after acute Nx. Thus, a significant reduction in $FR_{dist}$ in remnant nephrons occurred. Glomerular hyperfiltration and the described tubular reabsorptive adjustments together contributed to urinary volume flow and sodium excretion rates that were not different from those in the intact kidneys. These findings demonstrate the compensatory adaptations that play an essential role in the maintenance of body fluid homeostasis after acute Nx.

Our reabsorptive data obtained in surface proximal convoluted tubules by in vivo micropuncture techniques in the rat are in agreement with those results recently obtained in isolated, superficial proximal straight tubular segments perfused in vitro 24 h after unilateral nephrectomy in the rabbit (25), in which fluid volume reabsorption rate was demonstrated to be increased and closely related to GFR. However, they are in marked contrast to previous micropuncture studies (28) reporting a fall in $FR_{prox}$ with APR remaining constant and distal absolute reabsorption increasing by ~ 38% coincidentally with a ~ 12% increase in SNGFR, within 2 h of partial infarction of a single, already hypertrophied kidney. Whether the differences between the studies are related to the timing of micropuncture and/or to the fact that the effect of acute Nx on tubular function in the latter study was assessed in already hypertrophic remnant nephrons remains to be answered. Conflicting data have also been reported by another laboratory (29). The systemic and nephron responses 15 h after unilateral nephrectomy were characterized by a ~ 20% increase in MAP, increased SNGFR, decreased $FR_{prox}$, near-constant APR, and augmented $FR_{dist}$. The reason for the contradictory results remains to be identified, but it may arise from the differences in the mass of renal tissue removed or in the postsurgical volume status of the animals, or MAP, and thus renal perfusion pressure. Differences in MAP seem most likely, since in the latter study lowering of MAP to near control levels by aortic constriction normalized SNGFR and $FR_{prox}$ and prevented the natriuresis (29).

To test the hypothesis that the aforementioned early glomerular and tubular compensatory adaptations antecede nephron hypertrophy, DNA, RNA, and protein content were assessed in homogenates obtained from viable tissue in both remnant and intact kidneys. An increase in cell size (i.e., hypertrophy) is an invariable finding in the chronic state in remnant kidneys of mature animals. This structural change can be accurately ascertained by demonstrating an increase in protein and RNA content per dry tissue weight or in protein/DNA and RNA/DNA ratios (13). In the present study, renal DNA and protein content and protein/DNA were not affected but RNA content, and therefore RNA/DNA were slightly but significantly increased by ~ 10% at 24 h after acute Nx. These observations are in close agreement with previous studies using similar protocols (13). Earlier studies indicated that hypertrophy, while demonstrable in all segments of the nephron in chronic uremia, is most evident in the proximal tubule, which enlarges out of proportion to the rest of the nephron segments (3, 30). In the current study, tubular hypertrophy could not be confirmed by morphometric analysis 24 h after Nx. Together the results from this series of experiments indicate that although the process of compensatory hypertrophy may have already been activated, nephron hypertrophy is not established 24 h after Nx. This strongly argues against a role of hypertrophy as an important or necessary factor for the very early glomerular hemodynamic and tubular reabsorptive responses observed in this experimental model.

Without a structural change that could account for these functional adaptations, we considered the possibility that these adjustments were the consequence of hormonal–humoral actions in the nephrons at risk. Support for the possible importance of mediators with known vasoactive properties, in particular prostaglandin, being directly relevant to the acute hyperfunctioning state in remnant nephrons came from analysis of the urinary excretory rates of prostaglandin and from data obtained in other experimental studies performed in chronic Nx (12, 31, 32). In the present study, urinary excretory rates per nephron for 6-keto-$PGF_{1\alpha}$ and $TXB_2$, the stable metabolites of $PGI_2$ and $TXA_2$, respectively, were found to be approximately twofold higher in remnant compared with control kidneys. Considering the physiological roles of these mediators, it is possible that the primary effect of $PGI_2$ in regulating the renal microcirculation of the remaining kidney is to cause vasodilation (33) and therefore glomerular hyperfiltration. Prostaglandin may also participate in adjustments in solute and water reabsorption (34).

Finally, and perhaps more importantly, we determined in our second micropuncture protocol that prostaglandin synthe-

sis inhibition reversed the hyperfiltering state associated with acute Nx. Infusion of indomethacin, an inhibitor of cyclooxygenase activity, reduced within 1 h the baseline urinary excretory rates for 6-keto-$PGF_{1\alpha}$, $PGE_2$, and $TXB_2$ by ~ 80% in both remnant and intact experimental kidneys. These results suggest that the renal synthesis of these prostaglandins was markedly inhibited by indomethacin. In sham-operated rats neither MAP nor glomerular or tubular function were modified by the acute inhibition of these cyclooxygenase-dependent products. These observations confirm previous data (11, 15) and are consistent with the prevailing notion that in a baseline physiologic euvolemic state prostaglandins do not appear to influence nephron function. However, important differences between control and remnant nephrons in their response to prostaglandin synthesis inhibition was observed. Prostaglandin synthesis inhibition resulted in normalization of SNGFR and invariably prevented dilation at the afferent site, but it failed to alter efferent arteriolar tone in remnant nephrons. The apparent lack of an effect of prostaglandin synthesis inhibition on postglomerular vascular tone is certainly intriguing. Although the action of and interplay between other hormonal–humoral systems (10) in mediating the vascular adjustments in remnant nephrons cannot completely be excluded from the current results, the data strongly suggest that one of the vasodilatory prostaglandins conceivably $PGI_2$, influences preglomerular vascular sites, overcoming any potential effect of vasoconstrictor prostaglandin (i.e., $TXA_2$). By removing the vasodilatory influence of prostaglandin in remnant nephrons, normalization of SNPF and $\Delta P$ occurred. Thus, the net result of acute Nx is a vasodilatory prostaglandin-dependent effect on the remnant nephrons. This idea is consistent with a previous investigation (11) showing that vasodilatory prostaglandins are, in part, responsible for the glomerular hemodynamic adaptations in remnant nephrons 3–4 wk after Nx, and indicates, moreover, that this adaptation begins within 24 h after Nx. Those studies also reported that prostaglandin synthesis inhibition partially reversed the glomerular hyperfiltration and increased both $R_A$ and $R_E$, attenuated glomerular hyperperfusion, reduced LpA, and maintained glomerular hypertension (11). Although there might be several reasons for the modest discrepancies between those results and our own, the following appear to be the most reasonable: the elapsed time between Nx and micropuncture measurements (24 h vs. 3–4 wk) and thus the absence or presence of (*a*) structural hypertrophy, (*b*) systemic hypertension, and (*c*) a state of chronic renal failure. Nevertheless, it is now clear that, prostaglandins are important early mediators in the nephron adaptations associated with Nx.

Coincident with normalization of the filtered load in remnant nephrons during prostaglandin synthesis inhibition, APR was reduced to values not different from controls. This simultaneous and parallel reduction of APR and SNGFR indicated that glomerulotubular balance remained intact in remnant nephrons during the acute inhibition of prostaglandin synthesis. Normalization of $P_E$ and $P_i$ was also observed. Although $\pi_i$ was not estimated in this second series of experiments and therefore $P_{ER}$ and LpAr could not be calculated, it is reasonable to speculate that this Starling force may have been adjusted upward to or toward a normal level; thus the net result of all these adjustments would be a normalization of $P_{ER}$. The data suggest that in remnant nephrons even during prostaglandin synthesis inhibition adaptations in APR may be causally related to changes in SNGFR. In remnant nephrons $FR_{dist}$ tended to be higher in the experimental period in which prostaglandin synthesis inhibition was achieved as compared with baseline values. This change in reabsorption occurring between the late proximal and early distal micropuncture sites may represent an adaptation to the reduction in the amount of filtered load reaching the distal segments. Although recent micropuncture studies suggest that prostaglandin may inhibit water, sodium, and potassium reabsorption in distal tubular segments and chloride transport in the thick ascending limb of Henle (34), the experiments described herein cannot distinguish between these two mechanisms. Finally, it is noteworthy that treatment of nephrectomized rats with indomethacin significantly decreased the urinary volume flow to a rate lower than that measured in sham-operated rats.

In conclusion, the data reported in this communication may provide an important missing link in the pursuit of an understanding of the events leading to nephron hyperfunction. Clearly, these studies provide direct evidence that nephron hyperfunction is an early adaptation to acute Nx. This adaptive response, which cannot be ascribed to compensatory hypertrophy, appears to be the consequence of enhanced synthesis of cyclooxygenase-dependent products. The biologic relevance of the prostaglandin-mediated compensatory adjustments in function of the remnant nephrons is the preservation of body fluid homeostasis in the very early stage of this experimental model of chronic renal failure. We believe that the results of these studies suggest at least two new, fruitful areas of investigation: the first would be to determine the signal that translates acute Nx into an increased synthesis of prostaglandin, and the second would be to examine the contribution, if any, of increased prostaglandin synthesis to the eventual development of structural hypertrophy.

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