SUMMARY Glomerular hemodynamics were studied by micropuncture technique in the unclipped kidney in rats in which modest two kidney Goldblatt hypertension was maintained for 4 weeks and in normotensive controls. Both groups ingested less than 2 mEq Na+/day. In hypertensive rats at micropuncture, mean hydrostatic pressure was elevated both systemically (128 ± 5 vs 113 ± 3 mm Hg, p < 0.05) and within glomerular capillaries (55 ± 2 vs 48 ± 1 mm Hg, p < 0.05), resulting in an increase in the transglomerular hydrostatic pressure gradient (40 ± 2 vs 33 ± 1 mm Hg, p < 0.05). The glomerular capillary permeability coefficient, however, was decreased in the hypertensive rats (0.063 ± 0.017 vs 0.115 ± 0.011 nl/s/g kw/mm Hg, p < 0.05), resulting in no change in nephron filtration rate (38.9 ± 2.3 vs 39.9 ± 2.5 nl/min/g kw). Nephron plasma flow also remained unchanged (154 ± 10 vs 140 ± 7 ml/min/g kw). In separate studies in this model of hypertension, saralasin infusion demonstrated a peripheral effect of circulating angiotensin II which was increased over controls. Kidney mass and GFR were not different between clipped and unclipped kidneys. No consistent abnormalities were observed by light or electron microscopy either in glomeruli or in vessels in the unclipped kidney. This study demonstrates that glomerular hemodynamics may be altered early in the course of modest hypertension in this model without altering blood flow or filtration rate. The decrease in glomerular capillary area and/or permeability (LpA) in the hypertensive rats could be either a result of the increased effect of circulating angiotensin II or the direct effect of glomerular capillary hypertension.

KEY WORDS • Goldblatt hypertension • nephron filtration rate • glomerular capillary pressure

In several micropuncture investigations in the rat, systemic hypertension has been reported to be associated with glomerular hypertension and a reduction in the glomerular permeability coefficient.1-4 In much of this work, marked chronic systemic hypertension has produced significant secondary focal glomerular damage, coexisting with focal "superfunctioning" glomeruli. Thus, experimental findings in these models may be influenced by the process of compensatory glomerular hypertrophy. We therefore attempted the present micropuncture study, which examines glomerular pressures, flows, resistances, and permeabilities in the unclipped kidney 4 weeks after moderate systemic hypertension was established in the Goldblatt hypertensive Munich-Wistar rat. This study was undertaken 4 weeks after hypertension was established to minimize the effects of both focal glomerular obsolescence and other structural changes in the glomeruli studied, e.g., segmental sclerosis and/or glomerular hypertrophy. In this way we sought to define the initial glomerular adaptations to systemic hypertension in a model exhibiting the moderate increases in blood pressure which are most frequently encountered in clinical populations.

Methods

Male Munich-Wistar rats were used; they weighed 180 to 200 g (80-90 days old) at the start of the experiment. This strain of rat, raised and housed in an isolated colony at the Veterans Administration Medical Center, San Diego, California, characteristically provides from three to eight surface glomeruli accessible to micropuncture. Three groups of rats were studied at micropuncture; rats in which right renal artery stenosis was surgically produced (Group 1, n = 7); rats that were sham-operated (Group 2, n = 6); and rats that served as dietary controls (Group 3, n = 6). The latter group was studied to determine
whether the sham operation contributed either to the development of hypertension or to functional alterations in the contralateral kidney at micropuncture. Four additional groups of rats in which histologic and saralasin infusion studies were respectively performed are described later in this section.

Balance Studies

The degree of hypertension that develops in the two-kidney Goldblatt hypertensive rat is variable and may be accompanied by sodium retention or natriuresis.* Therefore, it appeared desirable to delineate the specific characteristics of this model in our hands. Balance studies and serial blood pressure monitoring were performed in both a group of 16 clipped rats, four of which were included in Group 1, and in a group of eight sham-operated rats separate from Group 2. After 7 to 10 days for acclimation to the diet and metabolic cages, control Na⁺ and K⁺ balance data were gathered over 1 week. Balance studies were then continued for 4 weeks after either production of renal artery stenosis or sham operation. A basic electrolyte-deficient liquid diet was used. The diet contained approximately 2 g of protein, carbohydrate, fat, amino acid supplements, trace elements, and full vitamin requirements per daily portion; Na⁺ and K⁺ were then added to 2-liter quantities of this diet. Each animal was provided 40 ml of a semisolid diet containing 2 mEq Na⁺, 2 mEq K⁺. Water intake was otherwise ad libitum. Specific Na⁺ and K⁺ intakes were then calculated from the volume of diet consumed. All urine and feces were collected over 3- to 6-day periods for each of the 5 weeks of study (control plus 4 postclip or post-sham weeks). Urine volumes were determined by weight. Urine Na⁺ and K⁺ concentrations were determined by flame photometry (Instrumentation Laboratories, Lexington, Massachusetts). Fecal Na⁺ and K⁺ were determined by the method of Leneen et al. Since fecal Na⁺ and K⁺ content was negligible for 42 balance periods studied, the remaining fecal samples were not analyzed and assumed to be zero. Balance data from each week was expressed as an average daily net gain or loss of Na⁺ and K⁺ for that week. Animals were weighed at least twice a week and always at the beginning and end of a balance period. Weight change for each week of study was expressed as the average increase or decrease per day. All rats studied at micropuncture were also maintained in metabolic cages and received the same diet as rats included in the balance studies.

Blood Pressure

In all animals in the balance studies, arterial pressure was measured 2–3 times per week by tail-cuff arteriosonde (NARCO Bio-Systems, Houston, Texas). Caged animals were pretrained for 30 minutes and then placed in a uniformly heated restraining chamber. The arteriosonde device was calibrated to its internal standard on each day of measurement. Diastolic pressures cannot be determined accurately by this method; therefore, only systolic pressures are reported for the 5 weeks prior to micropuncture.

Method of Clip Application and Sham Operation

Renal artery stenosis was produced in Goldblatt hypertensive animals by application of a silver clip made by bending silver ribbon (0.006 × 0.070 inches) over a wire template. Clips of 0.35 mm internal diameter were applied to the proximal right renal artery after carefully separating the artery from the renal vein utilizing a dissecting microscope. The procedure in sham-operated animals was identical except that no clip was placed. The dietary controls were surgically untouched. Only animals in which hypertension developed were included in the study, necessitating rejection of approximately 15% of clipped animals. This decision was based upon a statistically significant increase in awake blood pressure from the control, preclip week to the fourth week, the week prior to micropuncture.

Micropuncture Protocol

The left kidney was studied at micropuncture in Groups 1, 2, and 3. Groups 1 and 2 were studied 4 weeks after either application of the renal artery clip or sham operation. Animals were prepared for micropuncture as described previously. Throughout the study period, mean arterial pressure was determined via a femoral artery catheter. 14C inulin was dissolved in a physiologic NaCl-NaHCO₃ maintenance solution which was infused continuously through an indwelling jugular venous catheter at a rate of 0.6% b.w./hr (30–40 C/hr). Right and left (whole) kidney glomerular filtration rate (GFR), single nephron GFR (SNGFR), and afferent and efferent arteriolar protein concentration (Cₐ and Cₑ), respectively, were determined as described previously. Hydrostatic pressures were measured directly in glomerular capillaries (P₀), proximal tubules (P₇), and efferent arterioles (HPₑ) by methods described in detail in prior publications. To evaluate the influence of circulating angiotensin II (AII) in this model, the AII antagonist saralasin was infused in a separate (fourth) group of eight clipped rats under conditions identical to those obtained during micropuncture in Groups 1, 2, and 3. As in these latter three groups, a 1-hour equilibration period was allowed after surgical preparation, then several control mean arterial pressures (MAP) were obtained over a period of 1 hour. A saralasin infusion was begun at 1 μg/kg/min, and after 15 minutes, several measurements of MAP were again performed over the next hour. Saralasin was also infused utilizing an identical protocol in a fifth group of eight rats which were studied 4 weeks after a sham operation, at which time no renal artery clip was placed. The fall in MAP during saralasin infusion in the fourth and fifth groups of animals was calculated as the difference.
between the average control value and the average value obtained during the infusion of saralasin.

Histologic Studies

Tissue for light and electron microscopy was obtained from both a sixth group of six rats with renal artery clips 0.25 mm in external diameter and a seventh group of five sham-operated controls. As with the previous micropunctured groups, tissue studies were undertaken 4 weeks after clipping or sham operation. Systolic arterial pressure in the clipped rats (Group 6) as measured by the tail cuff method was increased an average of 21 ± 6 mm Hg during the postclip period (p < 0.01). No balance studies or micropuncture measurements were attempted in rats from which renal tissue was obtained for morphological analysis.

Light microscopy was performed in hematoxylin and eosin and periodic acid Schiff-stained paraffin sections of Bouin’s-fixed renal tissue. Transmission electron microscopy was done on uranyl acetate and lead citrate-stained sections (500-700 Å) of EPON 812 (Ladd Research Laboratories, Burlington, Vermont) embedded tissue. The tissue for electron microscopic study was obtained by superficial wedge biopsy prior to disruption of the renal circulation, and was fixed immediately by dicing in chilled 2% phosphate buffered glutaraldehyde (pH 7.3).

Calculations

Reference should be made to previous publications12-14 for calculation of afferent and efferent on-cotic pressures (πa and πe, respectively), single nephron filtration fraction (SNFF), single nephron plasma flow (RPF), afferent and efferent arteriolar resistances (AR and ER, respectively), efferent effective filtration pressure (EFPe), and mean effective filtration pressure (EFP).

The glomerular permeability coefficient, LpA, was calculated from SNGFR, πa, πe, ΔP, and RPF by a computerized iterative process previously described in detail.18 Only when ΔP-πe>0, defining the state of filtration pressure disequilibrium, can a unique value for LpA be determined. If ΔP≈πe (filtration pressure equilibrium) a minimum value for LpA can be calculated by assuming that π rises along a glomerular capillary of unit length so that ΔP ≈ πe at its most efferent point.

Statistical Analysis

Measurements of blood pressure, weight, and sodium and potassium balance in the control and in each of the experimental weeks were compared utilizing two-way analysis of variance. Micropuncture data from each group were compared by means of an unpaired t test. Individual animal means were utilized when several measurements of a given parameter were available from a single rat.

Results

Balance Studies: Course of Blood Pressure Alterations

Data showing respective sodium balances and changes in weight during the control week and each of the 4 postclip weeks are presented in figure 1. Animals with renal artery clips became hypertensive after clip application and exhibited significant stable hypertension in each of the 4 postclip weeks. Thus, although systolic pressures were only modestly elevated, values obtained clearly differed from sham operated animals handled under an identical protocol. Over the 4 postclip weeks, the average increase in systolic pressure in the clipped animals was 23 ± 3 mm Hg (fig. 1).

Comparison to the control preclip week, clipped animals retained sodium in Week 4 (p < 0.05). However, there was no difference in sodium balances between shams and clipped rats utilizing respective values obtained in Week 4. Clipped animals demonstrated significant weight loss during postoperative Weeks 1 and 2; during these weeks no significant change in sodium balance was demonstrated. No significant change in potassium balance was noted in either group during any period of the study. Sham-operated animals did not lose weight and could not be demonstrated to have altered sodium or potassium balances during the study period. Average daily Na+ intakes in the control preclip period in clipped and sham rats were 1.9 ± 0.0 and 1.8 ± 1.0 mEq/day respectively (NS) and for the postoperative period were, for Week

![Figure 1](http://hyper.ahajournals.org/)

Figure 1. Changes in systolic blood pressure, net daily Na+ balance, and daily weight changes for both clipped and sham-operated rats during the control preoperative week and for the 4 postclip weeks prior to evaluation by micropuncture. C = control week.
Micropuncture Studies

There were no differences in any measurements at micropuncture between sham-operated animals (Group 2) and unoperated controls (Group 3). Data from Groups 2 and 3 were therefore combined and treated as from a single group, which is designated the control group in subsequent discussion of the micropuncture data.

In part because clipped kidneys exhibited variable reductions in mass in Group 1, no difference in mean kidney mass could be demonstrated between the clipped and the contralateral unclipped kidney (0.60 ± 0.10 vs 0.81 ± 0.10 g). Non-normalized whole kidney flow was often markedly reduced on the clipped side; the value of 0.58 ± 0.18 ml/min on the clipped side did not differ statistically from the value of 0.90 ± 0.10 ml/min on the unclipped side. Urine flow was often markedly reduced on the clipped side making accurate GFR determination difficult in this hydropenic condition. GFR normalized for kidney mass also was not significantly reduced on the clipped side as a result of renal artery clipping (however, it was numerically lower in six of seven studies). Total (right plus left) GFR in Group 1 (1.49 ± 0.23 ml/min) was similar to total GFR in the control group (1.56 ± 0.13 ml/min). Left kidney mass (unclipped, micropunctured side) in hypertensive animals was similar to that in controls (0.81 ± 0.10 vs 0.77 ± 0.03 g). In control animals, right and left kidney weight (0.77 ± 0.03 vs 0.77 ± 0.03 g), GFR (0.83 ± 0.06 vs 0.71 ± 0.08 ml/min), and GFR/g were virtually identical. As further evaluation of the possibility that compensatory hypertrophy occurred on the unclipped side, SNGFR and GFR on the unclipped side were respectively compared with the contralateral GFR by linear regression analysis. While the process of compensatory hypertrophy would have been expected to produce an inverse correlation between these two variables, no correlation was demonstrable. Finally, the absence of an increase on the unclipped side of SNGFR (not normalized for kidney mass) compared to SNGFR in sham-operated animals suggests that compensatory hypertrophy was minimal and not readily demonstrable in this mild form of Goldblatt hypertension. Obviously, the reduction in awake GFR

1, 1.3 ± 0.1 vs 1.4 ± 0.1; for Week 2, 1.8 ± 0.1 vs 1.7 ± 0.1; for Week 3, 1.9 ± 0.0 vs 1.7 ± 0.1 (all NS); and Week 4, 1.7 ± 0.2 vs 1.2 ± 0.1 mEq/day respectively (NS). Values for K+ intake were identical since the diet contained equal quantities of Na+ and K+.

### Table 1. Hydrostatic Pressures, Nephron Blood and Plasma Flow and Filtration Rate in Hypertensive Rats and Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP (mm Hg)</th>
<th>P0 (mm Hg)</th>
<th>P1 (mm Hg)</th>
<th>ΔP (mm Hg)</th>
<th>HP0 (mm Hg)</th>
<th>SNGFR (nl/min/g kw)</th>
<th>RPF (nl/min/g kw)</th>
<th>RBF (nl/min/g kw)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive (Group 1)</td>
<td>128 ± 5</td>
<td>55 ± 2</td>
<td>16 ± 1</td>
<td>40 ± 2</td>
<td>20 ± 2</td>
<td>38.9 ± 2.3</td>
<td>154 ± 10</td>
<td>315 ± 24</td>
</tr>
<tr>
<td>Control (Groups 2 and 3)</td>
<td>113 ± 3</td>
<td>48 ± 1</td>
<td>16 ± 1</td>
<td>33 ± 1</td>
<td>21 ± 1</td>
<td>41.3 ± 3.9</td>
<td>140 ± 7</td>
<td>292 ± 17</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.05)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean ± SEM values are given.

MAP = mean arterial pressure; P0 = glomerular capillary hydrostatic pressure; P1 = Bowman's space hydrostatic pressure; ΔP = hydrostatic pressure gradient across glomerular membrane; HP0 = efferent peritubular capillary hydrostatic pressure; SNGFR = single nephron filtration rate; RPF = single nephron plasma flow; RBF = single nephron blood flow; and NS = not significant.

### Table 2. Glomerular Resistances, Effective Filtration Pressures, and Permeability in Hypertensive Rats and Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>AR (109 dyn. sec-cm-6)</th>
<th>ER (109 dyn. sec-cm-6)</th>
<th>πA (mm Hg)</th>
<th>πE (mm Hg)</th>
<th>EFPa (mm Hg)</th>
<th>EFPe (mm Hg)</th>
<th>EFP (mm Hg)</th>
<th>LpA (nl/s/g/kw/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive (Group 1)</td>
<td>19.2 ± 2.7</td>
<td>10.3 ± 1.2</td>
<td>19.4 ± 1.4</td>
<td>30 ± 2</td>
<td>20.3 ± 2.5</td>
<td>9.6 ± 2.9</td>
<td>14.6 ± 3.0</td>
<td>0.063 ± 0.017</td>
</tr>
<tr>
<td>Control (Groups 2 and 3)</td>
<td>17.6 ± 1.0</td>
<td>9.2 ± 0.5</td>
<td>19.2 ± 1.2</td>
<td>32.3 ± 1.2</td>
<td>14.2 ± 1.3</td>
<td>1.1 ± 1.8</td>
<td>6.2 ± 0.8*</td>
<td>0.115 ± 0.011†</td>
</tr>
</tbody>
</table>

Mean ± SEM values are given.

* Maximum estimate of EFP at filtration pressure equilibrium.
† Minimum estimate of LpA at filtration pressure equilibrium."
in the clipped kidney was not of significant magnitude to stimulate contralateral compensatory hypertrophy.

A summary of data obtained at micropuncture is presented in tables 1 and 2 and figures 2 and 3. The profiles of mean arterial pressure, glomerular pressure, and peritubular capillary hydrostatic pressure in control and Group 1 rats are presented in figure 3. Mean arterial pressure at micropuncture averaged 128 ± 5 mm Hg in Group 2 and 113 ± 3 mm Hg in controls (p < 0.05). Glomerular pressure (P_G) was 55 ± 2 mm Hg in Group 2 and 48 ± 2 mm Hg (p < 0.05) in controls. There was no difference in peritubular capillary pressure (HP_E) between hypertensive and control groups (20 ± 2 vs 21 ± 1 mm Hg). Since Bowman's space hydrostatic pressure (P_Bs) was unchanged, ΔP, the transglomerular hydrostatic pressure gradient (P_G - P_Bs), rose in Group 1 as a consequence of the increase in P_G (fig. 2). SNGFR, however, was not increased in Group 1 when compared to controls (39 ± 2 vs 41 ± 3 nl/min/g kw, fig. 2). There was no change in either systemic oncotice pressure (π_s) (19 ± 1 vs 19 ± 1 mm Hg) or nephron plasma flow (RPF) (154 ± 10 vs 140 ± 7 nl/min/g kw). Single nephron filtration fraction in hypertensive rats was 0.25 ± 0.03 which was not different from control values (0.29 ± 0.02, p > 0.2). L_P, the glomerular permeability coefficient, decreased in the hypertensive group to 0.06 ± 0.02 nl/s/g mm Hg, a value significantly less than the minimum possible value for L_P in control rats (0.12 ± 0.01 nl/s/g mm Hg, p < 0.05). This decrease in L_P observed in Group 1 opposed the increase in ΔP in this group, maintaining SNGFR equal to SNGFR in the control group.

As would be expected, filtration pressure disequilibrium did not obtain in the control group, as ΔP (33 ± 1 mm Hg) approximated π_E (32 ± 2 mm Hg), defining the state of filtration pressure equilibrium, in which EFP_E does not differ from zero (EFP_E = 1 ± 2 mm Hg) but disequilibrium was present in the hypertensive rats (fig. 2).

As there was no difference in RPF or hematocrit (51.1% vs 52.2%) between Group 2 and controls, single nephron blood flow also did not differ (315 ± 24 vs 292 ± 17 nl/min/g kw). Therefore, no evidence was provided for glomerular ischemia in the nephrons studied in Group 1. No change in AR or ER could be demonstrated statistically, although both AR and ER were numerically increased in Group 1. In Group 1 animals no significant correlation by regression analysis existed between systolic arterial pressures measured during the balance study period and either P_G or L_P; similarly, there was no significant correlation between MAP measured at micropuncture and either of the latter parameters.

The fall in MAP over the 1 hour during which the AII antagonist saralasin was infused was significantly greater in clipped animals than in sham-operated animals (ΔMAP = 21 ± 3 in Group 4 vs 12 ± 2 in Group 5, p < 0.05). In clipped rats, MAP fell from 122 ± 7 to 94 ± 6 mm Hg (p < 0.001); and in sham rats, MAP decreased from 122 ± 9 to 108 ± 9 mm Hg.
(p < 0.001). Thus, the effect of circulating All as unmasked by saralasin was demonstrably increased relative to sham-operated controls in this model of clip hypertension.

Five (of six) experimental rats prepared for morphologic study became hypertensive. In the rat with the highest systolic pressure (averaging 161 mm Hg over the 4 weeks), light microscopic examination revealed definite glomerular abnormalities. The lesion was characterized by increased mesangial PAS-positive material, which in areas had a granular appearance. Mild focal interstitial cellular infiltration and fibrosis were seen. The small arteries and arterioles were variably hyperplastic, with frank fibrinoid necrosis seen in the walls of two arterioles.

Electron microscopic studies of the unclipped kidneys revealed definite abnormalities only in the one experimental animal with the light microscopic changes described above. Thickening of the mesangial stalk area was apparent. There was an increase in matrix with infrequent circumscribed electron-dense accumulations in the mesangial area. In summary, the morphologic changes in the glomeruli of the unclipped kidneys were minimal and largely confined to the mesangial areas. No definite abnormalities were consistently demonstrated in endothelial or epithelial cells, or in the thickness of the GBM. Functional and morphologic correlations in the unclipped kidney were not possible in this study, since the studies were performed in different groups of animals.

Discussion

This study has examined the potentially multiple influences of sustained Goldblatt hypertension upon glomerular ultrafiltration in the “unclipped” kidney, which is exposed to systemic hypertension. In this model hypertension arises from increased activation of the endogenous renin-angiotensin system, a well-characterized system of pathogenetic importance to renovascular, and possibly essential, hypertension. Modest increases in arterial pressure were produced and were associated with an elevation of glomerular capillary pressure and a decrease in the glomerular permeability coefficient, LpA, representing the product of capillary surface area (A) and local hydraulic permeability (Lp). SNGFR was unchanged in the hypertensive group due to the opposing effects upon the filtration process of the increase in ΔP and the decrease in LpA. There was no significant change in afferent or efferent resistance. These hemodynamic alterations were associated with a constant rate of glomerular blood flow and plasma flow.

The present findings are similar in some respects to those of Schweitzer and Gertz, who studied younger rats with relatively severe Goldblatt hypertension, established for 4 weeks. In these animals, P0, as indirectly measured by stop-flow technique, was increased in the unclipped kidney, and the ultrafiltration coefficient was decreased. AR was increased both to autoregulate SNGFR and possibly to partially “protect” the glomerular capillary from the effects of hypertension. As a consequence of increased RPF and increased P0, SNGFR (as estimated from early proximal tubular flow rates) was increased; these findings may have been at least in part a consequence of hypertrophy of the unclipped kidney, influenced both by the demands of normal growth in the juvenile rat as well as by the contralateral decrease in GFR. The major difference observed in the present study was that although directly measured values for P0 and ΔP were increased and LpA was decreased, there were no changes in SNGFR or RPF. The present study is also unique in that the effects of moderate rather than severe hypertension were investigated in the absence of either generalized histologic alterations or focal glomerular hypertrophy or sclerosis. The lower blood pressures in this model may have derived from the rather modest NaCl intake of these rats. Balance studies revealed both a rather low Na intake and no significant Na retention when compared to control rats (fig. 1).

Azar et al. have reported findings similar to those of Schweitzer and Gertz in a model of severe chronic hypertension in the rat. In these studies, however, hypertension was induced by a high salt diet administered over several months, and significant focal nephrosclerosis was evident at the time of the study. In the studies of Azar et al., an increase in P0 (and ΔP) and an increase in RPF appeared to maintain the greatly increased SNGFR in a population of surviving nephrons. These “superfunctioning” glomeruli have also been observed in the unclipped kidney exposed to the effects of Goldblatt hypertension. It therefore cannot be determined from these studies whether the elevated P0 was a secondary adaptive phenomenon in surviving, but probably diseased nephrons, or whether glomerular hypertension was a feature of the initial pathophysiologic process which then further contributed to glomerular injury. Heterogeneity in nephron filtration rate was not observed in our hypertensive rats, as the standard error in the measurement of SNGFR in Groups 1 and 2 were comparable. Thus, there is no evidence histologically or statistically that focal glomerular injury was present in our model. The present study thus suggests that P0 can be elevated as an initial or primary consequence of even modest systemic hypertension, and not solely as a late change consequent upon advancing nephrosclerosis. It would appear that changes in pre- and postglomerular resistances do not normalize P0 in the course of sustained hypertension in this model, and that, as a consequence, glomerular hypertension occurs. For reasons as yet unclear, these findings differ from those reported in Kyoto hypertensive rats in which P0 is normal and afferent and efferent resistances are increased.

In the present study, the glomerular capillary permeability coefficient was decreased in Group 1 but unchanged in normotensive control animals. An obvious speculation is that this decrease in LpA could have been either an effect of All or the result of the elevation of P0 alone. Somewhat against this former
possibility is the previous finding from this laboratory that in the plasma expanded rat, infusion of native rat All in amounts sufficient to decrease LpA also reduced RPF and SNGFR, and increased P o, AP, AR, and ER. In the present study, this full spectrum of effects upon pressures, flows, resistances, and the glomerular permeability coefficient was not observed. Comparison of these studies must be made cautiously, however, as it is unclear whether All infusion studies duplicate states in which All is endogenously generated. It remains conceivable that LpA could have been reduced entirely through an effect of endogenously generated circulating All upon mesangial contractile elements in the absence of histologic changes in the present study on light or electron microscopy.

On the other hand, it is conceivable that chronically elevated P o alone may eventually induce alterations in the glomerular capillary and/or mesangium, which may initially be expressed only as a decrease in LpA. Indeed, in a model of acute nephrotoxic renal failure, a reduction in the glomerular permeability coefficient has been demonstrated to proceed discernible ultrastructural change. Furthermore, a decrease in the glomerular capillary permeability coefficient or a thickening of the glomerular capillary have been found in varying animal models of hypertension. Ultrastructural studies in human hypertension of varying etiologies have also demonstrated basement membrane thickening in glomerular capillaries as the initial histologic glomerular lesion. In these various conditions, as in the present study, an increased glomerular hydrostatic pressure may well be the common hemodynamic factor producing a decrease in glomerular capillary area and/or permeability.

In summary, in the present study during mild Goldblatt hypertension, SNGFR and RPF remained normal and unchanged although glomerular hemodynamics were markedly altered. P o was elevated in spite of normal measurements for whole kidney and single nephron plasma flow and filtration rate, and the glomerular permeability coefficient (LpA) was decreased. Elevated glomerular pressure does not appear late in the course of systemic hypertension as a consequence of the emergence of a population of superfunctioning nephrons. The early increase in P o may be causally related to the reduction in LpA and may be of potential importance in the initiation as well as the progression of hypertensive glomerular disease.

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