Pathogenesis of Glomerular Injury in the Fawn-Hooded Rat: Early Glomerular Capillary Hypertension Predicts Glomerular Sclerosis

Jacob L. Simons, Abraham P. Provoost, Sharon Anderson, Julia L. Troy, Helmut G. Rennke, Deborah J. Sandstrom, and Barry M. Brenner

ABSTRACT

Fawn-hooded rats spontaneously develop focal and segmental glomerular sclerosis, systemic hypertension, and proteinuria at a young age. Micropuncture and morphological studies were performed in two inbred strains of fawn-hooded rats, FHH and FHL, with different susceptibilities to develop chronic renal failure. FHH rats have higher values for systolic blood pressure and proteinuria and more rapid development of focal and segmental glomerular sclerosis and subsequent chronic renal failure as compared with genetically closely related FHL rats. FHH and FHL strains and a Wistar control strain, WAG, were matched for age and were studied at 16 wk. FHH, FHL, and WAG-old (WAG-O) strains were matched for weight, and the last group was studied at 22 wk. WAG were also matched for weight to a young group of FHH rats (FHH-Y), and these were studied at 8 wk. In comparison with WAG and WAG-O rats, FHH and FHH-Y rats exhibited an increase in mean glomerular capillary hydraulic pressure (WAG, 52 ± 1 mm Hg; WAG-O, 47 ± 2 mm Hg; FHH, 60 ± 2 mm Hg; FHH-Y, 65 ± 1 mm Hg), whereas values in FHL animals were intermediate (56 ± 2 mm Hg). No significant differences in glomerular volume were found among groups. Moderate focal and segmental glomerular sclerosis developed in FHH and FHH-Y rats, with values for older FHH rats being significantly greater than those for WAG, WAG-O, and FHL animals. Thus, the genetically determined sensitivity to develop proteinuria, focal and segmental glomerular sclerosis, and chronic renal failure in fawn-hooded rats correlated with early evidence of glomerular capillary hypertension. By contrast, glomerular hypertrophy was not associated with and was not a prerequisite for early glomerular injury in fawn-hooded rats.

Key Words: Glomerular sclerosis, proteinuria, chronic renal failure, GFR, glomerular volume

For many years, experimental animal models have been studied to elucidate the potential mechanisms causing the progression of renal disease to end-stage chronic renal failure (CRF). In humans, glomerulosclerosis is usually present at the end stage as is hypertension and nonselective proteinuria (1). Animal models described include surgical removal and/or infarction of renal tissue with or without superimposed hypertension and difference in dietary protein content (2,3), administration of drugs or toxins (4), and induction of a diabetic state (5). In contrast to these induced models, focal and segmental glomerulosclerosis (FGS) develops spontaneously in certain rat strains, reflecting a genetic predisposition (6). The fawn-hooded (FH) rat constitutes such a hereditary model. These rats develop FGS spontaneously, together with systemic hypertension and proteinuria at a young age (7,8). Systemic hypertension and proteinuria increase further with age, and the progression of sclerosis results in premature death from end-stage renal failure (8). This rat strain therefore constitutes a unique model, because it may resemble intrinsic human kidney disease more closely than the various models of induced renal injury mentioned above.
We previously reported that FH rats exhibit whole-kidney hyperfiltration accompanied by normal effective RPF and normal total number of glomeruli (9). These findings suggested the presence of single-nephron (SN) hyperfiltration and, because of the non-elevated RPF rate and high filtration fraction (FF), elevated glomerular capillary hydraulic pressure (P\text{oc}) as the predominant cause of the hyperfiltration (9). Maneuvers known to decrease P\text{oc} in other animal models, such as low-protein diet (3) or angiotensin I-converting enzyme inhibition (1), minimize glomerular sclerosis and proteinuria and also prolong renal survival in FH rats (11,12). On the other hand, maneuvers known to further increase P\text{oc}, such as uninephrectomy (13,14) or high-protein diet (3), accelerate the development of proteinuria and renal failure in FH rats (11,15). These findings further support the hypothesis that P\text{oc} is elevated in FH rats.

In this study, we assessed glomerular hemodynamics in FH rats and related the findings to the development of early proteinuria and FOS. This was performed in combination with renal morphologic studies. Two separate inbred strains of FH rats (16) with different susceptibilities to the development of FGS were used.

MATERIALS AND METHODS

Animals

Two isogeneic strains of FH rats, differing in systolic blood pressure (SBP), proteinuria, and susceptibility to the development of CRF, were obtained by selective inbreeding. For inbreeding, animals were selected on the basis of differences in SBP level as measured by the tail-cuff method. Genetic homogeneity within each strain regarding the histocompatibility haplotype was confirmed in the 15th generation by skin transplantation tests. FH rats with the highest SBP were designated FHH, and those with the lowest were designated FHL. The FHH rats also showed the highest levels of proteinuria and the fastest development of CRF (16). FHH and FHL rats were bred by brother-sister mating at the animal facilities of Erasmus University.

Thirty-nine male rats were used in five experimental groups. Briefly, we used two groups of FHH rats of different ages together with one group of FHL rats and two groups of normotensive control Wistar (WAG) rats (Harlan, Zelst, The Netherlands). Groups FHH, FHL, and WAG were matched for age. FHH, FHL, and WAG-Old (WAG-O) animals were matched for body weight (BW), as were WAG and FHH-Young (FHH-Y) rats.

Beginning at the age of 12 wk, SBP and 24-h urinary protein excretion (U\text{Pv}) were monitored in groups FHH, FHL, and WAG and at age 7 and 21 wk in groups FHH-Y and WAG-O, respectively. SBP was measured indirectly by the tail-cuff method. Urine was collected from individual rats during a 24-h period. Glomerular hemodynamic and morphologic studies were performed at age 16 wk in FHH, FHL, and WAG animals and at age 8 and 22 wk in groups FHH-Y and WAG-O, respectively.

Micropuncture Studies

After anesthesia was induced with ethyl ether, rats were placed on a temperature-regulated micropuncture table and subsequently given Inactin (BYK Gulden, Konstanz Fed. Rep. Germany) (100 mg/kg body wt. ip). Temperature was monitored rectally and maintained at 37.0 ± 0.5°C. After tracheostomy, a left femoral artery catheter was inserted to monitor arterial blood pressure and to obtain blood samples. After a baseline blood sample was collected, the right jugular vein was cannulated for the infusion of plasma and inulin. The plasma volume of rats prepared for micropuncture is reduced by approximately 20% (17). In order to study the rats in an euvoletic state, isoncotic plasma obtained from normal adult Sprague-Dawley rats was infused iv at a rate of 0.1 mL/min to a total amount equal to 1% of the BW. Thereafter, plasma infusion was continued at a rate of 0.58 mL/h to maintain the hematocrit (Hct) constant. Inulin (10 g/dL) in 0.9% NaCl was infused iv at a rate of 1.2 mL/h. The bladder and the left ureter were catheterized. The left kidney was exposed and suspended on a lucite holder, with its surface illuminated and bathed with isotonic saline. A 60-min equilibration period was allowed after completion of the fast plasma infusion.

For calculation of single-nephron (SN) GFR, four to six exactly timed samples of fluid were collected from superficial proximal tubules for the determination of flow rate and inulin concentration. Three to six efferent arteriolar blood samples were obtained from superficial star vessels for the determination of protein concentration. Coincident with these collections and the hydraulic pressure measurements, arterial blood samples were obtained for the determination of Hct and plasma concentrations of inulin and protein and 10- to 20-min urine collections from the left kidney were obtained for the determination of flow rate and inulin concentrations. These measurements permitted the calculation of GFR by standard formulae.

Because FH and WAG rats lack superficial glomeruli, time-averaged hydraulic pressures were measured directly in efferent arterioles (P\text{es}) and in superficial proximal tubules under free-flow (P\text{f}) and stop-flow conditions (P\text{sw}) with a servo-null micropipette transducer system (Model 5A; Instrumentation for Physiology and Medicine, San Diego, CA). Stop-flow conditions were obtained by the injection of bone wax (Ethicon W-31G; Brigham and Women’s Hospi-
tal, Boston, MA) blocks into proximal tubules with a wax-blocking device (Research Instruments & Mfg, Corvallis, OR). At least three to four P_{fr} recordings in different nephrons, with a minimum duration of 2 to 4 min each, were obtained during each experiment. Glomerular capillary hydraulic pressure (P_{oc}) was calculated as: P_{oc} = P_{fr} + \pi_{sf} (18). The mean trans-capillary hydraulic pressure difference (\Delta P) was calculated as:

\[ \Delta P = P_{oc} - P_T. \]

The colloid osmotic pressure of plasma entering and leaving glomerular capillaries was estimated from values for protein concentration in femoral arterial (representing afferent arteriolar) and efferent arteriolar plasma by the equation derived by Deen et al. (19). The estimates of preglomerular (C_{A}) and postglomerular (C_{E}) protein concentration permit the calculation of single-nephron filtration fraction (SNFF). Femoral arterial plasma protein concentrations were measured separately during the microsampling period (C_{A}) and during micropressure measurements (C_{fr}). Glomerular capillary ultrafiltration coefficient (K_f), afferent and efferent arteriolar resistances (R_{A} and R_{E}), and glomerular capillary plasma flow rate (Q_{A}) were calculated by equations described previously (19).

Renal Morphology

After the completion of each experiment, the kidneys were perfusion fixed at the measured systolic arterial blood pressure for 2 to 3 min with 1.25% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4). Kidney and heart weights were noted. Two midcoronal slices, one of each kidney, of 2 to 3 mm thickness, were processed for light microscopic examination. Paraffin sections (3 \mu m thick) were stained with hematoxylin and eosin and with periodic acid–Schiff reagent.

The extent of glomerular damage was determined on periodic acid–Schiff-stained slides by counting, on two coronal sections, all glomerular profiles with segmental or global collapse of capillaries, with or without associated hyalin deposition and adhesion of the tuft to Bowman’s capsule. The extent of FGS was expressed as the percentage of glomeruli with sclerotic lesions.

The average glomerular tuft volume (V_0) for each animal was determined by the procedure described by Weibel (20). For this purpose, the mean glomerular random cross-sectional area (A_0) was determined on 50 systematically sampled glomerular tuft profiles by point counting at a final magnification of x200 with a 361-point ocular grid covering a 369,664-\mu m^2 microscopic field. V_0 was then calculated as V_0 = (\beta/k)(A_0)^{3/2}, where \beta = 1.38 and k = 1.1 are shape and size distribution coefficients, respectively (20).

Systemic and Renal Hemodynamic Parameters

Mean values for systemic and renal hemodynamic parameters are summarized in Table 1. Despite numerically higher values for mean arterial pressure

\[ \text{SBP in the awake condition. Values are mean} \pm \text{SE.} \]

![Figure 1](image-url)

Figure 1. SBP in the awake condition. Values are mean ± SE. \*P < 0.05 vs WAG, \#P < 0.05 vs WAG-0, and \#P < 0.05 vs FHL. Moderate systemic hypertension of similar level is present in FHH-Y and FHH rat groups. FHL and Wistar rats are normotensive.
Glomerular Hypertension in FH Rats

As compared with those for WAG rats. Values for $C_A$ and $C_{Wr}$ were identical in all groups, whereas $C_E$ and consequently $r_E$ were significantly higher in FHH rats as compared with WAG-O rats.

Despite less evident systemic hypertension during anesthesia, measurements of $P_{OC}$ revealed the presence of glomerular capillary hypertension in both FHH and FHH-Y animals (Figure 3). Values for $P_{OC}$ in FHH-Y rats were on average 5 mm Hg higher than pressures observed in FHH rats; however, this difference was not statistically significant. As a consequence of the increased $P_{OC}$, the mean transcapillary hydraulic pressure difference ($\Delta P$) was elevated in FHH and FHH-Y rats. $\Delta P$ values for FHH rats were on average 12 mm Hg higher than values in WAG-O rats matched for BW. A similar mean elevation of 13 mm Hg was found in FHH-Y rats compared with BW-matched WAG rats. $\Delta P$ values for FHL rats were on average 7 mm Hg higher than those for WAG-O rats. This value is intermediate compared with that for FHH and WAG-O animals.

Efferent arteriolar pressures tended to be lower in FHH and FHH-Y rats, but only values in FHH-Y rats were significantly lower compared with those in FHL, WAG, and WAG-O rats. Values for $K_e$, $Q_A$, and $R_e$ did not differ among groups, with the exception of the significantly higher $Q_A$ in FHL rats compared with that in age-matched WAG rats. Values for $R_e$ in FHH rats were twice those found in FHL rats and were also higher compared with those in FHL rats. Values for $R_e$ in FHH-Y rats were also increased significantly compared with those in FHL and WAG-O rats but were only numerically higher compared with those in BW-matched WAG rats.

**TABLE 1. Glomerular and systemic hemodynamic parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>$N$</th>
<th>MAP (mm Hg)</th>
<th>Hct (%)</th>
<th>GFR (mL/min)</th>
<th>SNGFR (nl/min)</th>
<th>SNFF</th>
<th>$C_A$ (g/dL)</th>
<th>$C_I$ (g/dL)</th>
<th>$C_{Wr}$ (g/dL)</th>
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<tbody>
<tr>
<td>WAG</td>
<td>8</td>
<td>120 ± 3</td>
<td>44 ± 1</td>
<td>1.19 ± 0.06</td>
<td>47 ± 1</td>
<td>0.29 ± 0.02</td>
<td>5.2 ± 0.1</td>
<td>7.4 ± 0.2</td>
<td>5.2 ± 0.1</td>
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<td>WAG-O</td>
<td>7</td>
<td>116 ± 2</td>
<td>47 ± 1</td>
<td>1.37 ± 0.06</td>
<td>52 ± 2</td>
<td>0.26 ± 0.03</td>
<td>5.0 ± 0.2</td>
<td>6.8 ± 0.3</td>
<td>4.7 ± 0.3</td>
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<td>FHH-Y</td>
<td>8</td>
<td>125 ± 3</td>
<td>44 ± 1</td>
<td>1.41 ± 0.09</td>
<td>63 ± 3</td>
<td>0.36 ± 0.01</td>
<td>5.1 ± 0.1</td>
<td>7.9 ± 0.2</td>
<td>5.2 ± 0.1</td>
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<td>FHH</td>
<td>8</td>
<td>123 ± 3</td>
<td>44 ± 1</td>
<td>1.57 ± 0.08</td>
<td>60 ± 4</td>
<td>0.34 ± 0.03</td>
<td>5.4 ± 0.2</td>
<td>8.2 ± 0.3</td>
<td>5.5 ± 0.2</td>
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<td>FHL</td>
<td>8</td>
<td>128 ± 2</td>
<td>45 ± 1</td>
<td>1.50 ± 0.06</td>
<td>55 ± 2</td>
<td>0.30 ± 0.01</td>
<td>5.4 ± 0.2</td>
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<td>5.4 ± 0.2</td>
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<td>NS</td>
<td>NS</td>
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<tr>
<td>WAG vs FHH-Y</td>
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<td>NS</td>
<td>NS</td>
<td>*</td>
<td>NS</td>
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<td>WAG vs FHL</td>
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<td>NS</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>WAG-O vs FHH-Y</td>
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<td>NS</td>
<td>NS</td>
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<td>FHH vs FHL</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>

*Values are mean ± SE. * $P < 0.05$ between pairs; NS, $P > 0.05$ between pairs. MAP, mean arterial pressure; $C_A$ and $C_I$, afferent and efferent arteriolar protein concentration; $C_{Wr}$, afferent arteriolar protein concentration during stop-flow measurement; $r_E$, afferent arteriolar oncotic pressure; $r_{Wr}$, efferent arteriolar oncotic pressure; $P_{OC}$, stop-flow pressure.
Morphologic Parameters

Data for morphologic studies are presented in Table 2. Kidney weight (KW) was significantly higher in FHH and FHL rats as compared with that in WAG rats of similar age. However, when compared with that in WAG-O rats of similar weight, no significant difference was found. The heart weight (HW) reflected the level of awake systolic blood pressure in the various strains and was greatest in FHH and FHL rats. Values for mean glomerular diameter (Vg) were not significantly different among groups (Figure 4) and remained in the normal range (24). The percentages of glomeruli affected by sclerosis were highest in FHH and FHH-Y animals, but only values in FHH rats were significantly higher than those in both groups of WAG and FHL rats.

DISCUSSION

In this study, we have examined glomerular hemodynamics as well as renal morphology in two strains of FH rats with different susceptibilities to develop systemic hypertension, proteinuria, FGS, and subsequent CRF. The FHH strain is characterized by high values for SBP, SNFGR, POC, RE, and proteinuria. These parameters were found to define susceptibility to progressive glomerular sclerosis, because they were not abnormally elevated in control WAG and WAG-O rats. Values were intermediate in the FHL strain, as were degrees of glomerular sclerosis and proteinuria. Values for glomerular volume were similar in all groups and remained far below those reported in rats with diabetes and remnant kidneys (24), thereby failing to support a pathophysiologic role for hypertrophy in the pathogenesis of FGS in FHH rats. Because rats were studied before the development of severe sclerosis, we feel confident that we did not underestimate the true value of hypertrophy as a consequence of retraction and scarring.

As in human essential hypertension, the precise cause of the spontaneous development of systemic hypertension in FHH rats is not well understood. It has been reported that FH rats have low plasma and intrarenal renin (25,26), low urinary kallikrein excretion and renal kallikrein content (25), increased urinary output of dopamine, norepinephrine, and homovanillic acid (27), altered urinary eicosanoid excretion (28), and altered volume homeostasis (29).

Because of the absence of surface glomeruli in FH rats, POC cannot be evaluated by direct techniques and the indirect stop-flow technique had to be used. Debate regarding the equality of the POC values estimated by the two approaches has been extensive. Data obtained from indirect stop-flow technique may slightly overestimate values obtained by direct measurement. The differences between stop-flow and free-flow measurements are due to a tubuloglomerular feedback (TGF) response to the blockade of the flow in the loop of Henle. However, differences are usually small and present only in approximately one half of the studies (30). Activation of the TGF induced by changes in the loop of Henle flow resulted in parallel changes in directly measured POC and Psr, confirming that differences in POC do reflect differences in POC (31). However, it could be argued that the significantly higher Psr values in FHH and FHH-Y rats, when compared with values in weight- and age-matched WAG controls, are only present under stop-flow conditions. Without fluid delivery, there is

<table>
<thead>
<tr>
<th>( x_A )</th>
<th>( x_I )</th>
<th>( x_F )</th>
<th>( P_{sr} )</th>
<th>( P_{oc} )</th>
<th>( \Delta P )</th>
<th>( P_0 )</th>
<th>( K_i )</th>
<th>( Q_A )</th>
<th>( R_A )</th>
<th>( R_E )</th>
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<tbody>
<tr>
<td>16 ± 1</td>
<td>28 ± 1</td>
<td>16 ± 1</td>
<td>36 ± 1</td>
<td>52 ± 1</td>
<td>13 ± 1</td>
<td>39 ± 1</td>
<td>16 ± 1</td>
<td>0.048 ± 0.003</td>
<td>160 ± 9</td>
<td>1.93 ± 0.15</td>
</tr>
<tr>
<td>15 ± 1</td>
<td>25 ± 2</td>
<td>14 ± 1</td>
<td>34 ± 1</td>
<td>47 ± 2</td>
<td>11 ± 1</td>
<td>36 ± 1</td>
<td>16 ± 1</td>
<td>0.066 ± 0.011</td>
<td>208 ± 24</td>
<td>1.56 ± 0.20</td>
</tr>
<tr>
<td>16 ± 1</td>
<td>32 ± 1</td>
<td>16 ± 1</td>
<td>49 ± 1</td>
<td>65 ± 1</td>
<td>13 ± 1</td>
<td>52 ± 2</td>
<td>12 ± 1</td>
<td>0.036 ± 0.001</td>
<td>180 ± 12</td>
<td>1.54 ± 0.10</td>
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<td>18 ± 1</td>
<td>34 ± 2</td>
<td>18 ± 1</td>
<td>43 ± 1</td>
<td>60 ± 2</td>
<td>12 ± 1</td>
<td>48 ± 2</td>
<td>14 ± 1</td>
<td>0.045 ± 0.004</td>
<td>182 ± 14</td>
<td>1.66 ± 0.21</td>
</tr>
<tr>
<td>17 ± 1</td>
<td>29 ± 2</td>
<td>16 ± 1</td>
<td>39 ± 1</td>
<td>56 ± 2</td>
<td>13 ± 1</td>
<td>43 ± 2</td>
<td>15 ± 1</td>
<td>0.053 ± 0.010</td>
<td>202 ± 8</td>
<td>1.59 ± 0.08</td>
</tr>
</tbody>
</table>

mean glomerular capillary hydraulic pressure; \( P_{sr} \), mean intratubular hydraulic pressure; \( \Delta P \), mean glomerular transcapillary hydraulic pressure difference; \( P_0 \), mean afferent arteriolar hydraulic pressure; \( K_i \), glomerular capillary ultrafiltration coefficient; \( Q_A \), glomerular capillary plasma flow rate; \( R_A \), afferent arteriolar resistance; \( R_E \), efferent arteriolar resistance.
complete suppression of the TGF and \( P_{SC} \) and \( P_{SF} \) reach maximal values. The observed difference could disappear under free-flow conditions if the TGF system were more active in FHH than in WAG rats. A comparison of the TGF response between both strains is needed to settle this argument.

A number of studies have used the stop-flow technique in strains of rats that do not have surface glomeruli (30), among them another hypertensive strain, the spontaneously hypertensive rats (SHR). Comparison of SHR with the normotensive Wistar-Kyoto rat revealed no significant differences in \( P_{GC} \) between these strains (32,33). Thus, the SHR differs from the FHH with regard to the regulation of their glomerular hemodynamics. The presence of a normal \( P_{GC} \) in SHR might explain the finding that, in contrast to mildly hypertensive FH rats, SHR with a markedly higher blood pressure level do not develop proteinuria and renal lesions at a young age (34). The glomeruli in young SHR rats appear to be protected from high SBP by afferent vasoconstriction. However, when uninephrectomy is performed (35) or when older SHR are studied (36), afferent vascular tone decreases, \( P_{GC} \) rises, and progressive FGS and CRF ensue.

The glomerular capillary hypertension present in FHH rats results from increased efferent arteriolar resistance in the absence of increased afferent vascular tone. The moderate systemic hypertension is thus transmitted into the glomerular capillaries, and

![Figure 3. Glomerular capillary hydraulic pressure (\( P_{GC} \)). Values are mean \( \pm \) SE. \( * \) \( P < 0.05 \) vs WAG, \( \theta \) \( P < 0.05 \) vs WAG-O, \( \Delta P < 0.05 \) vs FHL. Values for \( P_{GC} \) were elevated in FHH rats of all ages and were significantly higher than those for both WAG groups. FHL rats exhibited slightly increased values for \( P_{GC} \), which were only significantly higher as compared with those for WAG rats matched for BW.](image)

![Figure 4. Glomerular tuft volume (\( V_{G} \)). Values are mean \( \pm \) SE. No significant differences in glomerular volume were found among groups.](image)

**TABLE 2. Morphologic parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age (wk)</th>
<th>BW (g)</th>
<th>Kidney Wt (g)</th>
<th>Heart Wt (10^6 ( \mu )m^3)</th>
<th>FGS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAG</td>
<td>8</td>
<td>16</td>
<td>282 ± 5</td>
<td>2.75 ± 0.08</td>
<td>0.82 ± 0.02</td>
<td>1.39 ± 0.07</td>
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<tr>
<td>WAG-O</td>
<td>7</td>
<td>22</td>
<td>340 ± 3</td>
<td>3.14 ± 0.10</td>
<td>0.95 ± 0.02</td>
<td>1.58 ± 0.03</td>
</tr>
<tr>
<td>FHH-Y</td>
<td>8</td>
<td>8</td>
<td>253 ± 9</td>
<td>3.21 ± 0.10</td>
<td>0.96 ± 0.03</td>
<td>1.62 ± 0.04</td>
</tr>
<tr>
<td>FHH</td>
<td>8</td>
<td>16</td>
<td>322 ± 5</td>
<td>3.64 ± 0.19</td>
<td>1.23 ± 0.09</td>
<td>1.65 ± 0.07</td>
</tr>
<tr>
<td>FHL</td>
<td>8</td>
<td>16</td>
<td>327 ± 14</td>
<td>3.45 ± 0.14</td>
<td>1.14 ± 0.04</td>
<td>1.55 ± 0.07</td>
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</table>

* \( * \) \( P < 0.05 \) between pairs; NS, \( P > 0.05 \) between pairs.
because of the high $R_e$, the pressure is retained in this network. The differences in SBP measured between animal groups in the awake condition were largely dissipated under anesthesia during the micropuncture experiments. It is therefore likely that $P_{oc}$ values are even higher in nonanesthetized FH animals. Evidence for a fundamental role of glomerular capillary hypertension in the progression of renal disease has been established in various other animal models (2-5,10,14). This study suggests that this hemodynamic maladaptation also contributes to the development of FGS in FHH rats.

Only a few studies in rats with spontaneous development of proteinuria and FGS, which may represent human progressive renal disease more closely than intervention models, have been reported. Remuzzi and coworkers recently described the spontaneous development of proteinuria, FGS, and hypertension in the male Munich-Wistar Frontier rat (37). $P_{oc}$ was elevated, suggesting that it may have again been the main factor responsible for these pathologic changes. Selective reduction of this pressure by converting enzyme inhibition resulted in protection against glomerular damage, restoration of glomerular permselectivity, and increased hydraulic membrane permeability (37). Brandis and colleagues suggested that, in rats of the Milan Normotensive Strain, proteinuria and FGS occur as a consequence of alterations in intrarenal hemodynamics, in particular, elevation of $P_{oc}$ (38). Genetically similar animals of the Milan Hypertensive Strain are protected from glomerular capillary hypertension and consequent glomerulosclerosis, possibly because of thickening of the interlobular arteries, which increases $R_A$ and thereby prevents the transmission of systemic hypertension into the glomeruli.

Kreisberg and Karnovsky first described the spontaneous occurrence of FGS in FH rats (7). Affected glomeruli were randomly distributed in the renal cortex, with no preferential localization to the juxtamедullary area. The earliest morphologic changes were noted at the age of 6 months and consisted of extensive changes in glomerular epithelium, including foot process fusion, vacuolization, bleb formation, and focal detachment from the glomerular basement membrane. The degree of epithelial cell damage and loss of glomerular polyanion correlated with the amount of proteinuria observed. Antibody-mediated injury was not present. These authors concluded that epithelial cell damage initiates a cascade of glomerular damage and proteinuria, eventually resulting in FGS. The importance of an intact podocyte population for the maintenance of glomerular function was emphasized by Fries and coworkers (39). In a model of progressive glomerulosclerosis induced by adriamycin and renal ablation, the degree of FGS and proteinuria was to a great extent directly related to epithelial cell injury and density. Kriz and coworkers suggested that glomerular capillary hypertension may cause distension of capillary loops when the system responsible for the creation of counteracting wall tension fails (40). The resulting capillary dilation is then thought to reduce the relative density of visceral epithelial cells. According to this formulation, epithelial cells eventually fail and the resulting denuded portion of glomerular basement membrane creates an area for increased protein convection, which results in further glomerular damage and eventually glomerulosclerosis. Because in the FHH rat we find that elevated glomerular hydraulic pressure predicts the subsequent development of FGS whereas significant increase of the glomerular tuft volume does not, epithelial cell damage must result from factors other than simple stretching of podocytes over an expanded glomerular tuft area.

In conclusion, this study establishes the presence of glomerular capillary hypertension, hyperfiltration, and exaggerated postglomerular resistance as early occurrences in FHH rats. Furthermore, we were able to demonstrate that these adaptations predict the genetically determined propensity to develop proteinuria, FGS, and CRF. FHH and FHL rat strains thus constitute a new model for progressive CRF caused by glomerular hypertension, the latter attributable directly to enhanced efferent arteriolar resistance. The basis for this early postglomerular vascular abnormality, whether structural, functional, or both and whether genetically predetermined, merits further study.

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