Renal Ablation Acutely Transforms ‘Benign’ Hypertension to ‘Malignant’ Nephrosclerosis in Hypertensive Rats

Anil K. Bidani, Karen A. Griffin, Wanda Plott, Melvin M. Schwartz

Abstract The present studies examine the consequences of the hemodynamic changes associated with ≈5/6 renal ablation in the spontaneously hypertensive rat (SHR), a strain that normally does not exhibit evidence of vascular and/or glomerular injury until late in life despite significant hypertension. Control SHR with intact renal mass demonstrated normal renal autoregulation and an absence of vascular or glomerular injury. Renal mass reduction resulted in an initial expected decrease in renal blood flow to the remnant kidney at 5 days (2.8±0.3 mL/min) compared with control SHR (8.1±0.7 mL/min) at a mean arterial pressure of approximately 160 mm Hg (P<.01). By 10 to 14 days after renal ablation, marked vasodilatation was observed (renal blood flow 8.3±0.5 mL/min at mean arterial pressure of ≈160 mm Hg) along with severe impairment of autoregulatory ability. Striking and florid vascular injury to interlobular arteries and afferent arterioles had also developed by 10 to 14 days after ≈5/6 renal ablation in a pattern similar to that observed in “malignant” hypertension, despite systolic blood pressures that were not significantly different from those in control SHR (168.2±6.4 versus 165.6±4.7 mm Hg). An additional group of SHR that were made normotensive with a triple-therapy antihypertensive regimen before and after ≈5/6 renal ablation also exhibited hemodynamic changes similar to those in the untreated rats at 10 to 14 days but did not develop significant vascular or glomerular injury. These data suggest that the vasodilatation and loss of protective autoregulation associated with ≈5/6 renal ablation result in the acute transmission of preexistent hypertension to the renal vasculature and the rapid development of severe vascular injury. 

Key Words • hemodynamics • hypertension, malignant • nephrosclerosis • nephrectomy

The non–stroke-prone spontaneously hypertensive rat (SHR) is generally considered to be a model of essential hypertension.1,2 As in humans, hypertension gradually increases in severity with advancing age, and evidence of target-organ injury does not develop until later in life (=12 months).3-5 We and others have previously demonstrated that ≈5/6 renal ablation in normotensive rat strains results in vasodilatation of the preglomerular remnant vasculature and an impairment of renal autoregulatory ability.6-8 Intact autoregulatory mechanisms result in proportionate preglomerular vasoconstriction in response to increases in systemic pressure and prevent these increases from being transmitted to the renal microvasculature, thereby protecting against hypertensive renal microvascular injury.5,9-11 We performed the present studies to examine the consequences of an acute impairment in renal autoregulation produced by ≈5/6 ablation in hypertensive rats and to correlate the pattern and severity of hypertensive injury with the evolution of hemodynamic changes in this model. We reasoned that if autoregulatory mechanisms are important in preventing acute glomerular and vascular injury in hypertensive SHR with intact renal mass,5,10 then an impairment of these mechanisms as a result of renal ablation should result in the acute development of hypertensive renal microvascular injury.

Methods

Experimental Design

Adult male SHR (8 to 12 weeks old, Harlan Sprague Dawley) were used in the present studies. The animals were housed in a constant-temperature room with a 12-hour light/dark cycle and cared for in accordance with the principles of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The protocols for these studies were approved by the Institutional Animal Care and Use Committee. All animals had free access to drinking water and rat chow. They underwent sham ablation or ≈5/6 renal ablation (right nephrectomy and ligation of all but one extrarenal branch of the left renal artery) as previously described.6,7 The rats were fed a standard protein (22%) and standard salt (1% NaCl) diet. Rats with remnant kidneys (RK) underwent renal blood flow (RBF) and autoregulatory studies at 5 days (RK-5d) or 10 to 14 days (RK-12d) after ablation to define the temporal course of renal hemodynamic changes and their relation to morphological injury. Renal hemodynamic and morphological studies were performed at approximately the 20th day after sham ablation in control SHR. An additional group of SHR was treated with a triple-therapy antihypertensive regimen (200 mg hydralazine, 5 mg reserpine, and 50 mg hydrochlorothiazide per liter of drinking water) (RK-TT-12d). After the initiation of the antihypertensive treatment, systolic blood pressure (BP) was measured every other day, and if satisfactory BP control (systolic BP <150 mm Hg) was not achieved (4 of 12 rats), the doses of hydralazine and reserpine were doubled. After 1 week of satisfactory BP control, the rats...
underwent 5/6 renal ablation. BP was monitored twice a week after renal ablation and the antihypertensive dose increased as above if necessary to maintain systolic BP below 150 mm Hg. Final renal and hemodynamic studies were also performed in this RKTT-12d group at 10 to 14 days after renal ablation. Tail-cuff systolic BP, serum creatinine (S_c), and 24-hour urinary protein excretion rates were measured at baseline (preablation) and before autoregulatory studies (postablation). After the hemodynamic studies were completed, the kidneys were harvested for morphological studies.

Systolic BP was measured with an occlusive tail cuff (model B60 type sensing cuff amplified by an ITTC model 59 amplifier from Life Sciences) and recorded with a Bausch and Lomb Omniscribe Recorder (Houston Instruments) as described previously. This procedure was performed in a warm, quiet room on trained, restrained, unanesthetized animals and yielded reproducible readings.

**Autoregulatory Studies**

Rats were anesthetized with sodium pentobarbital (40 mg/kg IV) through the tail vein, and a tracheostomy was performed using PE-200 tubing. A carotid artery and femoral artery were cannulated with PE-50 tubing. These cannulas were connected to a digital pressure recorder (WindoGraf, model 40-8474, Gould Instruments) for continuous recording of mean systemic and renal perfusion pressure. A femoral vein was cannulated with PE-50 tubing and used for administration of fluids or additional anesthetic. Through a midline incision, the left kidney was exposed and RBF (in milliliters per minute) was measured by a flowmeter (Transonic Systems) using a 2.0-mm Transonic R series flow probe placed around the left renal artery as previously described. At the completion of surgery, an intravenous bolus injection of 1% albumin in 150 mmol/L saline equal to 1% of body weight was administered and followed by a continuous intravenous infusion of the same solution at 3 mL/h to replace surgical losses and maintain euvolemma. Renal autoregulatory studies were performed approximately 30 minutes later by measuring the changes in RBF in response to graded reductions in mean arterial pressure (MAP) produced by an aortic miniclamp placed above the left renal artery. In each animal, the miniclamp was released in a stepwise fashion, and renal perfusion pressure was allowed to increase back to baseline in a graded fashion. The RBF results are the averages of the RBF response at each perfusion pressure as it was changed in both directions.

**Morphological Studies**

Kidneys from ablated and sham ablated rats were processed for light microscopy by standard methods as previously described. A coronal slice of the kidney through the papilla was embedded in paraffin; 4-μm sections were cut and stained with hematoxylin and eosin and periodic acid–Schiff (PAS). Sections were evaluated systematically in each kidney for glomerular and vascular lesions.

Vascular injury was measured by counting the number of vessels with morphological evidence of injury in a single section from each rat. At 5 days, this consisted of fibrinoid necrosis with segmental areas of eosinophilic granular degeneration of the media, with loss of smooth muscle nuclei, intense PAS positivity of individual muscle cells, and some perivascular myointimal proliferation. By 10 to 14 days, such evidence included fibrinoid necrosis, inflammatory cell infiltration in the media, and/or intramyocardial fibrosis (onion-skin), thrombosis, and aneurysm formation with perivascular hemorrhage and fibrosis. The number of vascular profiles with evidence of such injury for individual rats was then expressed as vascular profiles with injury per 100 glomeruli in the section and averaged for each experimental group (see below) for the differences in the amount of renal parenchyma present in individual tissue sections from these remnant kidneys with variable degrees of tissue hypertrophy. An attempt was made to identify and separately quantify the individual segments of the renal microvasculature that exhibited hypertensive lesions, ie, arcuate and interlobular arteries or afferent arterioles. However, such identification was not always possible because of the severity of the destructive lesions. Glomerular injury was measured by enumerating the total number of glomeruli in the section as normal, ischemic, acute hypertensive injury, or segmental sclerosis.

Normal glomeruli were defined by the appearance of the glomeruli in the kidney of the sham-operated SHR. The capillary loops were patent; there were no segmental lesions or adhesions; and mesangial cellularity was limited to no more than three cells per mesangial area. The surrounding tubules were intact, and there was no periglomerular fibrosis. Ischemic glomeruli had smaller, shrunken tufts; collapsed or greatly reduced capillary lumens; and wrinkled, folded glomerular basement membranes. The associated tubules were atrophic, and periglomerular fibrosis was present. Acute hypertensive injury was indicated by fibrinoid necrosis of part or all of the glomerular tuft. This process frequently extended into the glomerulus from an involved arteriole, and it was accompanied by capillary thrombosis, karyorrhexis, leakage of fibrin into Bowman's space, and proliferation of the parietal epithelium of Bowman's capsule. These acute changes involved the glomerulus in either a segmental or global fashion. Segmental glomerular sclerosis consisted of collapse of the involved portion of the glomerulus with obliteration of the capillary lumina. These changes were frequently accompanied by a fibrous adhesion between the glomerular tuft and Bowman's capsule.

The number of glomeruli exhibiting the different patterns of injury was expressed as a percentage of the total number of glomeruli in the section and ranged from 0% to 20%. A total of 60 to 400 glomeruli were present in the sections for each animal. For the purpose of this quantitation, the ischemic-looking glomeruli around the edges of the infarct were excluded, but those in the apparently functioning remnant renal tissue were included.

**Analyses, Calculation, and Statistics**

S_c was measured by an autoanalyzer (Beckman Instruments). Urinary protein was measured by the quantitative sulfosalicylic acid method with human serum albumin serving as standard. Autoregulatory index (AI) was calculated by the method of Semple and deWardener:  

\[ AI = \frac{[IBP_l - IBP_f]}{IBP_l} \times \frac{[RPP_1 - RPP_2]}{RPP_1}, \]

where RPP is the renal perfusion pressure calculated as (MAP – RVP), with RVP being the renal venous pressure assigned a value of 5 mm Hg.

All results are mean±SEM. Statistical analysis was performed using ANOVA and repeated-measures ANOVA followed by Student-Newman-Keuls multiple comparison test.  

A value of \( P < .05 \) was considered nonsignificant.

**Results**

Table 1 presents the data for body weights, systolic BP, S_c, and urinary protein excretion for the four SHR groups investigated. The only significant difference among these groups was the significantly lower BP in the RKTT-12d group as a result of the treatment \( (P < .05) \). Renal ablation resulted in significant increases in S_c in all RK groups \( (P < .01) \) so that the S_c in all RK groups after ablation was significantly greater than in control SHR after sham ablation \( (P < .05) \). Within the RK group the S_c at 10 to 14 days in both treated and untreated rats was significantly lower than in the RK-5d group, probably a reflection of the compensatory increases in renal function (see below). Urinary protein excretion and BP both increased significantly by 10 to 14
days after \( \approx 5/6 \) renal mass reduction in the RK-12d group \( (P<.05) \) but were not significantly different from values in sham ablated SHR. However, it should be noted that proteinuria originated from only approximately one sixth of the nephrons in the RK-12d group.

Fig 1 illustrates the time course of the hemodynamic changes and autoregulatory responses of RBF to graded reductions in renal perfusion pressure in the four SHR groups. Renal ablation resulted in an initial marked decrease in absolute blood flow to the remnant kidney so that RBF in the RK-5d group was significantly lower than in the intact left kidney of sham ablated SHR at all MAP values (Fig 1). By 10 to 14 days after renal mass reduction, there was a large increase in blood flow to the remnant renal tissue so that the total RBF in RK-12d rats was comparable to and not significantly different from that of the intact kidneys of sham ablated SHR above an MAP of approximately 120 mm Hg and was significantly greater than the RBF in RK-5d rats at all MAP values. The RBF values in the treated RKTT-12d group were intermediate to those in the RK-5d and RK-12d groups and were significantly lower than sham rats but not significantly different from RK-12d rats below an MAP of approximately 140 mm Hg.

Examination of the autoregulatory responses of RBF to changes in MAP within each group (Fig 1) showed that the sham control rats demonstrated significant autoregulatory reductions in renal vascular resistance with each change in MAP between 160 and 120 mm Hg so that the RBF was maintained. However, RBF decreased significantly when MAP was further reduced from approximately 120 to approximately 100 mm Hg. In contrast, RBF declined significantly in both the RK-12d and RKTT-12d groups after graded reductions in MAP through the entire range of approximately 160 mm Hg to approximately 100 mm Hg because of a lack of significant autoregulatory changes in renal vascular resistance. The RK-5d rats were more heterogeneous, with some animals essentially maintaining RBF constant despite changes in perfusion pressures and others exhibiting progressive declines in RBF with decreases in MAP. This resulted in small and statistically nonsignificant decreases in mean RBF for the group with such decreases in MAP.
AUTOREGULATION INDICES

\[ \begin{align*}
\bar{AP} < 120 \text{ mmHg} & \quad \text{Sham (n=8)} \\
\bar{AP} > 120 \text{ mmHg} & \quad \text{RK-5d (n=8)} \\
& \quad \text{RK-12d (n=7)} \\
& \quad \text{RKTT-12d (n=8)}
\end{align*} \]

Fig 2. Bar graph shows calculated autoregulatory indexes for changes in renal blood flow (Fig 1) after graded changes in mean arterial pressure (\(\bar{AP}\)) above and below approximately 120 mm Hg in spontaneously hypertensive rats (SHR) after sham ablation or \(\approx 5/6\) renal ablation (RK). Studies in the RK group were performed 5 days (RK-5d) and 10 to 14 days (RK-12d) after renal ablation and at 10 to 14 days in SHR that had received a triple-therapy antihypertensive regimen before and after renal ablation (RKTT-12d). *Significantly different from sham control, \(P<.01\).

RK-12d groups were not statistically significant. Below a perfusion pressure of approximately 120 mm Hg, all groups autoregulated poorly, and there were no significant differences among the groups (Fig 2).

Morphology Results

Figs 3 through 6 illustrate the renal morphology in the four groups, and Table 2 presents the semiquantitative scores for vascular and glomerular injury in the four SHR groups.

Sham Ablated Rats

The sham ablated control SHR had well-preserved, normal-appearing renal cortex without evidence of vascular or glomerular injury (Fig 3).

RK-5d Rats

Five days after \(\approx 5/6\) ablation there was extensive infarction of renal tissue resulting from the vascular ligation procedure to reduce renal mass. Glomeruli with ischemic changes and atrophic tubules were only seen around the margins of the infarcted tissue. Acute vascular injury with fibrinoid necrosis was present in 9 of 10 animals but was very focal and only involved a few vessels in each section (Table 2, Fig 4A). It was most prevalent in the large, proximal arcuate and interlobular arteries, with only 4 of 10 animals showing similar lesions in the arterioles. The lesions were characterized by granular, homogeneous, eosinophilic degeneration of the vascular wall with loss of architectural detail and smooth muscle nuclei. In longitudinal sections of arteries, the lesion was clearly segmental (Fig 4B). These areas were intensely PAS positive, and focal PAS positivity in individual cells of otherwise uninvolved arteries suggested early injury (Fig 4C). Karyorrhectic debris associated with these foci and occasional arcuate or interlobular arteries with perivascular fibroelastic proliferation suggesting early aneurysm formation supported the interpretation that these were early signs of necrosis. These changes have been previously described in the literature as "atypical" vascular necrosis and attributed to acute stretching of the vasculature.\(^16\)

Three of 10 rats had glomerular fibrin and platelet thrombi in 2%, 3.5%, and 10% of their glomeruli. However, there was no evidence of glomerular capillary necrosis or scarring.

RK-12d Rats

In animals examined 10 to 14 days after ablation, the focal lesions of fibrinoid necrosis seen after 5 days were largely replaced by more prevalent and severe lesions of acute hypertensive injury (Fig 5A, Table 2). Necrotizing lesions of arcuate arteries were present in 4 of 9 animals with fibrinoid necrosis and neutrophilic infiltration of the media and perivascular inflammation (Fig 5B). Injury to the interlobular arteries was much more extensive than in animals studied at 5 days and consisted of fibrinoid necrosis of the vessel wall, thrombosis,
myointimal proliferation (onion-skin) (Fig 5C), microaneurysm formation, and perivascular hemorrhage and fibrosis. In addition to the severe injury to these proximal vascular segments that was present in all animals, there was also evidence of involvement of more distal vascular segments in 7 of 9 rats that exhibited similar injury to arterioles (Fig 5D). Despite the severity of vascular lesions, evidence of direct hypertensive

Fig 4. Photomicrographs show vascular pathology in a spontaneously hypertensive rat 5 days after &gt;5/6 renal ablation. A, Glomeruli and tubules are well preserved. Interlobular artery (asterisk) has a segmentally thickened eosinophilic wall with smudging and loss of smooth muscle nuclei (hematoxylin and eosin, original magnification ×175). B, Longitudinal section of interlobular artery with periodic acid–Schiff (PAS)–positive homogeneous degeneration in the wall at a branch point extending into the smaller vessel (PAS, original magnification ×175). C, Interlobular artery with PAS positivity of individual cells (arrows) (PAS, original magnification ×650).

Fig 5. Photomicrographs show glomerular and vascular pathology in a spontaneously hypertensive rat 12 days after &gt;5/6 renal ablation. A, Severe vascular damage with preservation of the glomeruli (arrows) and tubules. There is fibrinoid necrosis of an arteriole (asterisk) and proliferation of surrounding connective tissue (double asterisks) (hematoxylin and eosin, original magnification ×175). B, Arcuate artery with extensive necrosis, infiltration of media by neutrophils, and perivascular inflammatory reaction (hematoxylin and eosin, original magnification ×65). C, Interlobular artery with thrombosis of the lumen and concentric proliferation of connective tissue elements in the damaged vessel walls (hematoxylin and eosin, original magnification ×260). D, Thrombosis and necrosis of the efferent arteriole (arrow), extending into the glomerulus (asterisk). The intense perivascular reaction is a longitudinal view of the proliferative process illustrated in panel C (periodic acid–Schiff, original magnification ×130).
injury to the glomeruli was also noted in only 4 of 9 rats, and it was very focal and usually limited to the extension of a necrotic arteriolar lesion into the glomerulus (Fig 5D). Ischemic glomeruli were present not only at the margins of the infarct, but were also scattered throughout the damaged tissue in proximity to severely injured blood vessels.

**RKTT-12d Rats**

In contrast, SHR made normotensive before renal ablation and maintained normotensive after renal ablation showed no evidence of vascular injury (Fig 6), although an occasional glomerulus in a few rats exhibited changes of ischemia, sclerosis, or hypertensive injury (Table 2).

**Discussion**

Morphological hypertensive injury to the renal microvasculature in both humans and experimental animals has been broadly separated into two patterns. The pattern described as benign nephrosclerosis is the more frequent and comprises slowly progressive arteriosclerosis and ischemic changes in the glomeruli without evidence of active and acute injury. In contrast, the acute lesions of fibrinoid necrosis and/or thrombosis of the interlobular arteries, arterioles, and glomerular capillaries typically observed with more extreme (malignant) hypertension have been intuitively attributed to the severity of hypertension and termed malignant nephrosclerosis. The results of the present study clearly demonstrate that factors in addition to the severity of systemic hypertension are important determinants of such acute hypertensive injury. Severe and dramatic renal vascular and microvascular injury in a pattern typical of malignant nephrosclerosis was observed within 2 weeks of 5/6 renal ablation in the present study, with systemic pressures not significantly different from those of control SHR with intact renal mass. This implies that renal ablation must have resulted in an increase in the intravascular pressures in the vascular segments that developed acute hypertensive injury. The progressive vasodilation and impairment of renal autoregulatory ability that followed =5/6 ablation by 10 to 14 days provide a plausible explanation.

**TABLE 2. Morphological Results**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Injured</th>
<th>Ischemic</th>
<th>Acute HTN Injury</th>
<th>GS</th>
<th>Vascular Injury Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham control (n=8)</td>
<td>0.1±0.05</td>
<td>0</td>
<td>0</td>
<td>0.1±0.05</td>
<td>0</td>
</tr>
<tr>
<td>RK-5d (n=10)</td>
<td>1.6±1.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.8±0.9*</td>
</tr>
<tr>
<td>RK-12d (n=9)</td>
<td>9.9±4.0††</td>
<td>8.9±3.6††</td>
<td>1.0±0.5</td>
<td>0</td>
<td>19.6±3.9††</td>
</tr>
<tr>
<td>RKTT-12d (n=12)</td>
<td>2.0±1.2</td>
<td>0.9±0.6</td>
<td>0.2±0.1</td>
<td>1.0±0.9</td>
<td>0</td>
</tr>
</tbody>
</table>

HTN indicates hypertension; GS, glomerulosclerosis. Animal group definitions as in Table 1. Glomerular injury shows percent of glomeruli exhibiting injury. Vascular injury score is the number of vascular profiles with injury per 100 glomeruli in the section (see "Methods" for details). Vascular injury at 5 days consisted of segmental areas of fibrinoid necrosis in the vascular wall with eosinophilic granular degeneration of media and loss of smooth muscle nuclei. Vascular lesions in the RK-12d group were more typical of severe acute hypertensive injury and included fibrinoid necrosis with inflammatory cell infiltrates in the media and/or the intima, onion skin, thrombosis, and aneurysm formation with perivascular hemorrhage and fibrosis. Glomerular lesions of RK-5d rats consisted of fibrin and platelet thrombi without evidence of glomerular capillary necrosis in three rats. See text for details.

*P<.05, †P<.01 vs sham control.
†P<.05 vs RK-5d or RKTT-12d.
for such a change in the intravascular pressure profile of the renal vasculature.

RBF autoregulatory ability was noted to be preserved in the SHR with intact renal mass in the present study, as has also been noted in previous studies. Although the primary objective of renal autoregulation is generally considered to be maintenance of constant glomerular filtration rate despite changes in renal perfusion (systemic) pressure, renal autoregulatory resistance changes are also expected to prevent increases in microvascular pressures and flows from occurring downstream from the autoregulatory sites despite increases in perfusion (systemic) pressures. Consistent with this interpretation, micropuncture studies in SHR with intact renal mass have demonstrated the predicted autoregulatory increases in preglomerular vascular resistance and maintenance of normal glomerular pressures. The absence of glomerular injury in SHR with intact renal mass despite systemic hypertension provides support for the importance of autoregulatory mechanisms in protecting against hypertensive injury. A similar protective role has been ascribed to the normal autoregulatory mechanisms in other models of experimental hypertension as well as in human hypertension.

Although the mediators have not been definitively identified, the changes in renal hemodynamics observed after 5/6 renal ablation in SHR are similar to what has been described in normotensive rat strains. Although the increase in blood flow through the remnant circulation has been demonstrated to begin shortly after renal mass reduction, the present data suggest that the process is markedly accelerated between 5 and 10 to 14 days after 5/6 renal ablation in SHR. The progressive vasodilation in the face of systemic hypertension in the untreated SHR with renal ablation suggests that the vasodilator stimulus of renal mass reduction overrides the expected autoregulatory vasconstriction. This impairment of autoregulatory behavior in SHR with renal ablation was confirmed by the autoregulatory studies shown in Fig 1. The impairment was fully developed by 10 to 14 days in association with the development of marked vasodilation of the remnant vasculature in both treated and untreated SHR. The calculated AI values of approximately 1 in these groups at 10 to 14 days indicate that the remnant renal resistance vessels by this time behave as passive conduits. The impairment in autoregulatory ability is similar to that noted in other rat strains regardless of their susceptibility or resistance to the development of hypertension and/or microvascular injury after 5/6 ablation. Therefore, the impairment in autoregulation seems to be an invariable consequence of the 5/6 ablation—associated hemodynamic changes.

The vasodilation and loss of autoregulatory ability after 5/6 renal ablation was temporally associated with the rapid development of acute and severe renal vascular and microvascular injury. These data are consistent with the concept first advanced by the work of Pickering, Wilson, and Byrom and others that acute "malignant" hypertensive injury to target organs occurred primarily as a consequence of overperfusion rather than underperfusion and/or ischemia. The lack of significant injury in treated normotensive SHR despite similar 5/6 renal ablation indicates that the observed vascular and microvascular pathology in the untreated SHR with renal ablation is not a consequence of 5/6 renal ablation per se. Renal vasodilation and loss of renal autoregulation were present in these animals, similar to untreated SHR after 5/6 ablation, suggesting that the observed hemodynamic changes are insufficient to result in vascular and microvascular pathology in the absence of hypertension.

Some impairment of both autoregulatory ability and early vascular injury had begun soon after 5/6 renal ablation (RK-5d rats), but it is likely that the hemodynamic changes are the primary event. Qualitatively, similar hemodynamic and autoregulatory changes have been observed in normotensive rat strains after renal mass reduction, in which the changes precede the development of significant hypertension and/or microvascular injury. Moreover, the thrombotic and necrotic lesions observed at 10 to 14 days after renal mass reduction would be expected to increase resistance and thereby decrease RBF. Instead, a marked increase in RBF was observed. This is consistent with the still focal distribution of vascular injury at this time despite its qualitative severity. This interpretation does not exclude the possibility that the initial vascular injury may cause further impairment of autoregulatory ability and thereby contribute to additional vascular injury. Renal vasodilatation may have additionally contributed to the observed severity of vascular injury in SHR at 10 to 14 days after ablation. Dilated vascular segments have been previously demonstrated to be at a significantly greater risk for hypertensive injury. This may partly represent the adverse effects on the vascular wall by increased tension as predicted by the Laplace law (wall tension = pressure x radius). However, other as yet unknown factors associated with vasodilatation may also be involved.

The distribution of vascular injury in the present study may be a consequence of the order in which vasodilatation occurs in renal vascular segments after renal mass reduction in hypertensive rats. The lesion of "atypical" necrosis of arcuate and interlobular vessels was frequently observed at both 5 and 10 to 14 days after ablation. This lesion has been demonstrated to be an early consequence of acute hypertensive distention of the vasculature and often involves the larger muscular vessels. But at 10 to 14 days, lesions were predominantly observed in interlobular vessels and arterioles and to a lesser extent in the glomeruli. This distribution is consistent with a role for the participation or recruitment of protective myogenic mechanisms in the more proximal preglomerular vasculature of hypertensive rats and in keeping with several recent studies that have demonstrated myogenic autoregulatory responses in the interlobular and to a lesser extent in the arcuate vessels.

The pattern of morphological injury to the remnant renal microvasculature in the SHR is also different from that described in normotensive rat strains. At 2 to 3 weeks after similar 5/6 renal ablation, only mild and focal glomerular injury is observed in some animals, and vascular injury is infrequent. The differences in susceptibility to vascular injury may result from the different rates and/or patterns of exposure of the renal microvasculature to severe hypertension. Systemic hypertension develops gradually after 5/6 renal mass reduction in normotensive rat strains, whereas the pre-
existent hypertension in SHR results in more acute exposure of the renal vasculature and therefore perhaps more severe injury. This interpretation is supported by the data obtained by Tolins and Raij,40 who observed a similar pattern of severe vascular and glomerular injury after 5/6 ablation in hypertensive Dahl salt-sensitive rats.

In summary, the present studies show that the vasodilation and impairment of renal autoregulation that follow ≈5/6 renal ablation are associated with the acute transformation of preexistent "benign" hypertension to "malignant" nephrosclerosis. These data emphasize the importance of local protective autoregulatory mechanisms, in addition to the severity of hypertension, in the pathogenesis of acute hypertensive vascular and microvascular injury.

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References
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