Critical Blood Pressure Threshold Dependence of Hypertensive Injury and Repair in a Malignant Nephrosclerosis Model

Karen A. Griffin, Aaron Polichnowski, Natalia Litharg, Maria Picken, Manjeri A. Venkatachalam, Anil K. Bidani

Abstract—Most patients with essential hypertension do not exhibit substantial renal damage. Renal autoregulation by preventing glomerular transmission of systemic pressures has been postulated to mediate this resistance. Conversely, malignant nephrosclerosis (MN) has been postulated to develop when severe hypertension exceeds a critical ceiling. If the concept is valid, even modest blood pressure (BP) reductions to below this threshold regardless of antihypertensive class (1) should prevent MN and (2) lead to the healing of the already developed MN lesions. Both predicates were tested using BP radiotelemetry in the stroke-prone spontaneously hypertensive rats receiving 1% NaCl as drinking fluid for 4 weeks. Severe hypertension (final 2 weeks average systolic BP, >200 mm Hg) and MN (histological damage score 36±5; n=27) developed in the untreated stroke-prone spontaneously hypertensive rats but were prevented by all antihypertensive classes (enalapril [n=15], amlodipine [n=13], or a hydralazine/hydrochlorothiazide combination [n=15]) if the final 2-week systolic BP remained <190 mm Hg. More impressively, modest systolic BP reductions to 160 to 180 mm Hg (hydralazine/hydrochlorothiazide regimen) initiated at ≈4 weeks in additional untreated rats after MN had already developed (injury score 35±4 in the right kidney removed before therapy) led to a striking resolution of the vascular and glomerular MN injury over 2 to 3 weeks (post-therapy left kidney injury score 9±2, P<0.0001; n=27). Proteinuria also declined rapidly from 122±9.5 mg/24 hours before therapy to 20.5±3.6 mg 1 week later. These data clearly demonstrate the barotrauma-mediated pathogenesis of MN and the striking capacity for spontaneous and rapid repair of hypertensive kidney damage if new injury is prevented. (Hypertension. 2014;64:801-807.) • Online Data Supplement

Key Words: calcium channel blockers ■ hypertension ■ renal circulation ■ renin-angiotensin system

Hypertension-induced renal damage is second only to diabetic nephropathy as a primary cause of end-stage renal disease (ESRD). However, except for some genetically susceptible subgroups such as blacks, the majority of patients with essential hypertension exhibit a low individual risk of developing ESRD as is apparent when the relatively small prevalence of ESRD (<0.5%) is contrasted with the huge prevalence of hypertension in the general population. We and others have suggested that intact renal autoregulatory mechanisms in individuals with essential hypertension protect the glomerular capillaries from blood pressure (BP) elevations within the autoregulatory range so that only the slowly progressive vascular pathology of benign nephrosclerosis with late and modest ischemic nephron loss is observed. Severe renal damage in such individuals is usually only seen when they develop the syndrome of accelerated/malignant hypertension with severe systolic BP elevations (>200 mm Hg) presumably exceeding a critical threshold and resulting in a syndrome of malignant nephrosclerosis (MN) with acute disruptive vascular and glomerular injury, proteinuria, hematuria, and renal failure.

If such a formulation as to the pathogenesis of the MN pathology is valid, even modest BP reductions to below such a threshold should be able to prevent its development. The fact that salt-supplemented stroke-prone spontaneously hypertensive rats (SHRsp) exhibit preserved renal autoregulation before the development of MN renders the SHRsp model particularly suitable for an examination of these concepts. In addition, such BP reductions to below the critical threshold for injury, even after MN lesions have already developed, should nevertheless result in the repair/regression of such MN lesions, despite continued hypertension. However, this has not been directly demonstrated. Moreover, only limited data exist as to the fate of the already developed MN lesions when BP is subsequently reduced but without complete normalization as is often the case clinically. The present studies were performed to address these aspects of MN in the SHRsp model using BP radiotelemetry.
Table 1. Baseline Body Weights, Systolic BP, Proteinuria, and Final Body Weights and Proteinuria

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Body Weight, g</th>
<th>Systolic BP, mmHg</th>
<th>Proteinuria, mg/24 h</th>
<th>Body Weight, g</th>
<th>Proteinuria, mg/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% NaCl (27)</td>
<td>244±4.7</td>
<td>171.5±1.8</td>
<td>7.3±0.8</td>
<td>261±6.7</td>
<td>115.5±12.8</td>
</tr>
<tr>
<td>1% NaCl (15)+enalapril</td>
<td>262±5.4</td>
<td>176.2±2.2</td>
<td>5.6±0.4</td>
<td>301±2.7</td>
<td>24.3±3.1*</td>
</tr>
<tr>
<td>1% NaCl (15)+H&amp;H</td>
<td>249±4.6</td>
<td>173.6±2.1</td>
<td>6.3±0.7</td>
<td>295±5.0*</td>
<td>14.1±0.9*</td>
</tr>
<tr>
<td>1% NaCl (13)+amlodipine</td>
<td>247±6.1</td>
<td>175.3±2.1</td>
<td>6.2±0.6</td>
<td>282±6.2</td>
<td>22.2±2.4*</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; and H&H, a combined antihypertensive regimen of hydralazine and hydrochlorothiazide. *P<0.05 vs the untreated 1% NaCl only group. The final data at 4 wk for the untreated 1% NaCl groups include data obtained from 6 rats before the 4 wk who were euthanized for humane reasons between the third and fourth week.

Methods

Detailed methods are provided in the online-only Data Supplement. Two sets of studies were performed.

Protocol A (Prevention of MN by Modest BP Reductions)

Saline drinking SHRsp rats were randomly allocated to 1 of the 4 groups; they were left untreated or received 1 of the following 3 antihypertensive regimens for the following 6 weeks: enalapril 50 mg/L, amlodipine 50 mg/L, or a combination of hydralazine (100–200 mg/L) and hydrochlorothiazide (25–50 mg/L) in the drinking fluid (H&H).

Protocol B (Repair of MN Lesions After Modest BP Reductions)

Similar to the untreated rats in protocol A, male SHRsp were placed on a Japanese style diet and 1% NaCl for ≈3 to 4 weeks till they were noted to have a systolic BP >200 mmHg and a significant increase in proteinuria. The rats were then anesthetized and the right kidney removed to quantify the severity of existing renal damage. After uninephrectomy, the rats were continued on the same diet but additionally received the combination H&H regimen in the drinking fluid so as to maintain a systolic BP of <190 mmHg. The rats were followed for 2 (n=11) or 3 (n=13) weeks after which they were euthanized, and the remaining kidney was harvested to assess the extent of histological repair/regression. Five additional rats, which also underwent uninephrectomy at 3 to 4 weeks but did not exhibit significant pretreatment histological injury, were not included in the analysis.

Results

Protocol A Studies (Prevention of MN by Modest BP Reductions)

At baseline, there were no significant differences in body weight, 24-hour urinary protein excretion rates (<10 mg/24 hours in all groups), or average systolic BP between the groups (Table 1). However, the institution of the Japanese style diet and 1% NaCl as drinking fluid rapidly led to progressive increases in systolic BP (Figure 1). Coadministration of enalapril with the 1% NaCl as drinking fluid essentially abrogated such BP increases in all but 2 of 15 rats. By contrast, both the H&H combination and amlodipine were more effective and produced significant BP reductions from baseline that were maintained, despite the continued salt supplementation (Figure 1). The final body weights and protein excretion rates before euthanasia after 4 weeks are also presented in Table 1. Body weight was significantly lower in the more severely hypertensive untreated SHRsp, although the amlodipine-treated rats also tended to gain less weight for unclear reasons.

The increases in proteinuria in the 4 groups of rats after salt supplementation followed the same pattern as the BP response to salt supplementation, with severe increases only being seen in the severely hypertensive untreated SHRsp and the 2 of 15 enalapril-treated rats. Similarly, histological renal damage was also essentially confined to these same more severely hypertensive untreated and 2 of 15 enalapril-treated rats (Table 2). Substantial vascular and glomerular injury was observed, with glomerular ischemia being more prominent than glomerular fibrinoid necrosis and thrombosis. Segmental glomerulosclerosis (GS) was observed infrequently and was sometimes difficult to separate from acute necrotic injury. Therefore, for purposes of this quantification (Table 2), these 2 patterns of glomerular injury have been combined. Linear regression analysis was used to examine the quantitative relationship between BP and composite renal damage score in individual rats from all 4 groups. Although strong correlations were observed between BP parameters and the hypertension-induced renal damage scores, the threshold relationship between BP and renal damage was most clearly revealed when

Figure 1. Course of radiotelemetrically measured systolic blood pressure (BP). Weekly averages of radiotelemetrically recorded systolic BP (means±SEM) at baseline (week 0) and over the subsequent 4 weeks in the 4 groups of stroke-prone spontaneously hypertensive rats which received as drinking fluid (1) 1% NaCl, (2) 1% NaCl+enalapril, (3) 1% NaCl+ a combination of hydralazine and hydrochlorothiazide (H/H), and (4) 1% NaCl+amlodipine. The baseline BP was the average systolic BP during the past 3 days before the initiation of a Japanese style diet and salt supplementation. Six of 27 untreated rats were euthanized for humane reasons between the third and fourth week (see Methods for details). *P<0.05 maximum vs the untreated 1% NaCl only group, #P<0.05 maximum vs 1% NaCl+enalapril group.
the composite hypertension-induced renal damage score in individual rats was correlated with their average systolic BP during the final 2 weeks of the course (Figure 2). As can be noted, the slope of the relationship (increase in hypertension-induced renal damage score/mm Hg increase in systolic BP during the final 2 weeks) is essentially flat for systolic BP <190 mm Hg and increases sharply and linearly at systolic BP >190 mm Hg.

**Protocol B Studies (Repair of MN Lesions After Modest BP Reductions)**

Figure 3 presents the results of these studies. Because of the individual differences in the time to uninephrectomy (3–4.5 weeks), the group data for the weekly systolic BP averages and proteinuria are presented as at baseline, for the 2 to 3 weeks before uninephrectomy, and for 2 to 3 weeks after the initiation of antihypertensive therapy (AHT) with the H&H regimen. As can be noted, sharp increases in BP and proteinuria were observed during the final week before uninephrectomy. Acute reductions in systolic BP with AHT of ≈20 to 30 mm Hg to below the BP threshold noted in protocol A studies resulted in a rapid and dramatic decrease in proteinuria, which was sustained throughout the follow-up period.

Figure 4A to 4D provides a histological illustration of the acute hypertensive vascular and glomerular injury in the right kidneys of salt-supplemented SHRsp rats, which were removed before the initiation of the AHT and contrasts it with the much improved histology observed in the remaining left kidney at the termination of the studies after 2 to 3 weeks of H&H therapy. No significant differences were observed between the left kidneys of rats euthanized after either 2 or 3 weeks of AHT. Accordingly, the results have been combined for the presentation of the quantitative data (Figure 5). A striking resolution of vascular injury and glomerular ischemia was observed. A modest but significant decrease in the percentage of glomeruli exhibiting glomerular injury was also observed, and the lesions at this stage appeared to be predominantly sclerotic rather than necrotic.

**Discussion**

The precise pathogenesis of the progressive renal damage in individuals with essential hypertension continues to be investigated and debated. Although individuals with diabetic and nondiabetic chronic kidney disease (CKD) are generally acknowledged to exhibit an enhanced susceptibility to the adverse effects of even moderate hypertension,4–7 there is considerable controversy as to whether the benign nephrosclerosis pathology of essential hypertension causes ESRD in the absence of an enhanced genetic predisposition such as...
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Figure 4. Representative photomicrographs of right kidneys removed from rats on Japanese style diet and 1% salt drinking water before antihypertensive treatment (RK) and left kidneys remaining in rats on the same regimen after hydralazine and hydrochlorothiazide treatment (LK). Top Masson Trichrome), Arteriolosclerosis (arrowhead), glomerular necrosis (arrow), interstitial infiltrates, and fibrosis in RK but not in LK. Middle and Bottom (hematoxylin and eosin [H&E]). Arteriol necrosis and glomerular necrosis in RK (middle), proliferative occlusive arteriolosclerosis with red blood cells in arteriolar wall in RK (bottom), and arterioles with nearly normal morphology in LK (middle and bottom). Arrowheads indicate arterioles; asterisks, interlobular artery; LK, left kidney; RK, right kidney; and V, vein. Micron bar, 100 μm.

has been identified in blacks.2,3 By contrast, there is a general consensus that in the absence of adequate antihypertensive management, MN usually does progress to ESRD.7–12 However, controversy persists as to whether in addition to experimental hypertension.7–12,14–25 The present studies do not provide protection against MN with little or no BP lowering in the SHRsp model of MN.7,9–12,21–23 However, these studies had almost exclusively relied on tail-cuff BP measurements that have been demonstrated to be inadequate for such interpretations.26,27 When BP radiotelemetry was used in the SHRsp model, the protection by renin–angiotensin–aldosterone system blockers, aldosterone antagonists, and endothelin receptor blockade and depends less on BP reductions but more on the modulation of specific cellular/molecular pathways that include plasminogen activation inhibitor, matrix metalloproteinases, growth factor signaling, and so on.28–33 By contrast, the present data illustrate the considerable capacity for spontaneous repair of hypertensive renal injury if new hypertensive injury is prevented. Although some of these differences in results may represent differences in the mechanisms and sites of renal damage and repair in these models (vascular and arteriolar versus glomerular), they may also partly reflect the limitations of the tail-cuff BP measurements used in these previous studies for investigating the BP dependence of repair/regression. It is also worth emphasizing that the acuity and magnitude of the reduction in proteinuria within a week of the initiation of modest BP reductions suggest a functional rather than a structural repair against MN may depend on preventing the BP from reaching a critical threshold independent of the antihypertensive class because 3 different antihypertensive regimens were equally effective in protecting against MN, by maintaining BP below the critical threshold and within the described autoregulatory range for SHRsp rats (mean arterial pressure between 100 and ≈175 mm Hg).13

Such interpretations and the concept of a critical BP threshold for MN injury are further buttressed by the striking demonstration that BP reductions of 20 to 30 mm Hg to below such a threshold result in a dramatic resolution of the already developed MN lesions. Thus, the maintenance of a BP below the critical threshold may be both necessary and sufficient to not only prevent MN but also for the regression of the already developed MN lesions, although the precise mechanisms/pathways mediating such repair remain to be defined. In this context, it is of note that these data are in sharp contrast to previous studies that have found BP reductions with hydralazine-based regimens per se to be ineffective in achieving repair/regression of already developed renal pathology in the NMA-nitro-L-arginine methyl ester model of MN, as well as in the 5/6 renal ablation model.28–30 In general, these studies have concluded that producing regression of such renal lesions requires supramaximal doses of renin-angiotensin system blockers, aldosterone antagonists, and endothelin receptor blockade and depends less on BP reductions but more on the modulation of specific cellular/molecular pathways that include plasminogen activation inhibitor, matrix metalloproteinases, growth factor signaling, and so on.28–33 By contrast, the present data illustrate the considerable capacity for spontaneous repair of hypertensive renal injury if new hypertensive injury is prevented. Although some of these differences in results may represent differences in the mechanisms and sites of renal damage and repair in these models (vascular and arteriolar versus glomerular),
basis for at least the initial response. Given the previously demonstrated relationships between acute changes in glomerular pressure ($P_{gc}$) and proteinuria, it is possible that the initial reduction in proteinuria results from the restoration of the normal autoregulatory responses and $P_{gc}$ when BP is reduced into the autoregulatory range. In any event, the present data are consistent with past clinical data reporting recovery from dialysis requiring renal failure in patients with MN using nonspecific antihypertensives before renin-angiotensin system blockade was clinically available.

The success of modest BP reductions to 160 to 180 mm Hg in preventing MN is in sharp contrast to the apparent need for BP reductions into the normotensive range (systolic BP <140 mm Hg) to prevent progressive GS in CKD (reduced renal mass) models. The substantially different BP thresholds above which significant renal damage starts to develop in MN versus CKD models likely reflect differences in autoregulatory capacity and which probably also account for the differences in the histological pattern/phenotype of renal damage that is observed between MN and CKD models. In MN, a breach of the normal autoregulatory ceiling by the severe hypertension (systolic BP exceeding ≥200 mm Hg) results in an acute exposure of the downstream resistance vessels and microvasculature to high intravascular pressures and barotrauma. Accordingly, MN is characterized by evidence of acute disruptive injury to the intrarenal vasculature with distal glomerular ischemia and less frequently, active capillary injury as observed in the present study. Lesions of segmental GS are uncommon in MN. By contrast, segmental GS is the predominant lesion in CKD models, and acute vascular injury is usually not observed. It is likely that the more moderate hypertension in CKD states is insufficient to cause acute disruptive vascular injury but nevertheless exposes the glomerular capillaries to chronically increased local pressures because of the preglomerular vasodilation and impaired autoregulation, resulting in GS. These data also suggest that the threshold for hypertensive injury may differ between vascular segments (arteries and arterioles versus glomerular capillaries). Such intrinsic differences in the ability to withstand barotrauma may also be relevant to the issue of repair/regression of the hypertensive lesions after the initiation of AHT. Modest BP reductions of 20 to 30 mm Hg to below the critical threshold are expected to both promote vascular healing and also allow restoration of the autoregulatory mechanisms to protect glomerular capillaries from further barotrauma, although it is likely that the capacity for complete repair/regression may be more limited in glomerular capillaries.

These differences in the pathogenesis and anatomic distribution of the hypertensive injury in MN and CKD states may also be relevant to the differential effects of calcium channel blockers (CCBs) in these states/models. As in the present study, CCBs have also been noted to be protective in other MN models such as the SHR given Nω-nitro-L-arginine methyyster and the deoxycorticosterone acetate + salt model. Such data support the interpretation that vascular injury is primarily dependent on the increased vascular pressures and, therefore, is prevented and ameliorated by CCB-mediated BP reductions below the threshold for vascular injury. By contrast, CCBs may be less effective in protecting the glomerular capillaries from hypertensive injury. For instance, although amlodipine was successful in ameliorating the vascular injury in the deoxycorticosterone acetate + salt models, GS was not prevented. Similarly, despite their antihypertensive effectiveness in CKD models, CCBs do not consistently reduce proteinuria and GS in CKD models. We have postulated that this failure is because of the concurrent deleterious effects of CCBs on renal autoregulation. Although the systemic BP is reduced, a greater fraction of the BP is transmitted distally to the glomerular capillaries and glomerulopathy protection proportionate to the achieved BP reductions is not obtained. Consistent with such a postulate, using BP radiotelemetry, we have shown that the slope of the relationship between BP and GS is made steeper by CCB therapy in the 5/6 renal ablation model such that greater GS is observed at any given BP elevation in CCB treated as compared with untreated rats with remnant kidneys. These interpretations may also help explain the parallel clinical data showing the effectiveness and general equivalence of CCBs and other antihypertensive agents including RAAS blockade in preventing vascular events such as stroke and myocardial infarction. By contrast, CCBs, particularly dihydropyridine CCBs, have been noted to be less effective than RAAS blockade in slowing progression in proteinuric CKD states where the glomerular capillaries are the primary site of hypertensive injury.

**Perspectives**

The results of the present studies provide a potential explanation for the substantially greater success that has been achieved clinically with AHT in preventing MN compared with slowing the progression of CKD states. They additionally demonstrate the considerable capacity for vascular repair/healing after acute MN injury, even with relatively moderate systolic BP reductions to 160 to 180 mm Hg. These data thus suggest that the magnitude of protection provided by antihypertensive agents may depend not only on the magnitude of the BP reduction but also on the prevailing threshold and slope relationships between BP and renal damage in a given model, disease state, or individual. Conversely, for the same reasons, the contribution of any given BP increase to the observed renal damage may also differ between individuals. It also needs to be emphasized that although MN can be prevented by such BP reductions of 20 to 30 mm Hg to below the critical threshold, the long-term risk for benign nephrosclerosis and more importantly for other target organ damage continues with such suboptimally controlled hypertension. And it is of note that the risk of adverse cardiovascular events significantly exceeds that for progression to ESRD even in patients with pre-existent renal disease, emphasizing the importance of adequate BP control and the lack of clinically meaningful differences between antihypertensive agents for the prevention of such macrovascular events in most patients with essential hypertension.

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Disclosures
None.

References


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**What Is New?**

- These data demonstrate that a striking and rapid regression of acute hypertensive vascular and glomerular injury may be achievable with only modest blood pressure reductions.

- These salutary effects, independent of antihypertensive class, indicate a barotrauma-mediated pathogenesis of such acute hypertensive renal injury.

**What Is Relevant?**

- The variable effectiveness of antihypertensive agents in mitigating hypertensive renal damage may depend on the threshold and slope relationships between blood pressure and renal damage that may exist in individual hypertensive states.

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**Summary**

Modest blood pressure reductions independent of antihypertensive class to below a critical threshold are not only sufficient to prevent the development of malignant nephrosclerosis but even to result in a striking and rapid resolution of already developed acute hypertensive injury, despite substantial continued hypertension.
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THE CRITICAL BP THRESHOLD DEPENDENCE OF HYPERTENSIVE INJURY AND REPAIR IN A MALIGNANT NEPHROSCEROSIS MODEL

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METHODS

Animals and Animal Care: The SHRsp were obtained from a colony transferred to Hines, IL from the colony maintained at University of Michigan, Ann Arbor since 1981 and currently maintained at the Georgia Regents University, Augusta. Only male rats were used. They were cared for in accordance with the Principles of the Guide for the Care and Use of Laboratory Animals and housed in a constant-temperature room with a 12-hour light and 12-hour dark cycle with free access to standard rodent chow and tap water as drinking fluid. Protocols were approved by the Hines VA Institutional Animal Care and Use Committee.

Experimental Protocols: When the rats were ~10-12 weeks old (body weight ~225-275g), they were anesthetized (intraperitoneal sodium pentobarbital, 50mg/kg body weight), instrumented for radiotelemetric BP monitoring (Data Sciences International, Minneapolis, MN), as previously described, (BP sampled for 10 seconds, every 10 minutes for 24 hours/day). The data presented and analyzed are for systolic BP, given that it exhibits stronger correlations with renal damage and experimental data indicate that it serves as the trigger for the autoregulatory myogenic response. After 7-10 days of BP monitoring on a standard diet, the last 3 days of which were considered baseline, the rats were placed on a Japanese style rodent diet (Ziegler, PA) with a sodium and potassium content of 0.39% and 0.56% respectively and given 1% NaCl to drink so as to accelerate the severity of hypertension and target organ damage. Rats were periodically placed in metabolic cages for measurement of 24-hour proteinuria (sulfosalicylic acid and spectrophotometry). At the conclusion of the studies, the rats were anesthetized and the kidneys harvested after perfusion-fixation for histologic analysis as previously described.

Protocol A (Prevention of MN by modest BP reductions): Higher doses of hydralazine and hydrochlorothiazide were used initially (first 8 rats) but were then reduced for the subsequent 7 rats to moderate the achieved BP reductions. Of the untreated saline drinking rats, 6 of the 27 became very severely hypertensive (systolic BP >250 mmHg) with associated weight loss and were therefore euthanized for humane reasons during the 4th week prior to the planned conclusion of the studies. Accordingly, the terminal measurements in these rats were obtained at the end of the 3rd week, 2-4 days before euthanasia and are included as the final data in the presented results. Overt stroke was not observed.

Histologic Analysis: Glomerular and vascular damage was separately quantitated in a blinded fashion in transverse kidney sections (3-4μm) from both kidneys, stained with hematoxylin & eosin and periodic acid-Schiff as previously described. The glomerular damage score was calculated as the total percentage of glomeruli exhibiting lesions of (i) acute hypertensive injury (necrosis, thrombosis, microaneurysms) (ii) segmental glomerulosclerosis (collapsed capillaries with mesangial matrix expansion and/or hyalinosis); and (iii) ischemic injury (shrunk glomeruli with collapsed capillaries). Similarly, the vascular damage score was calculated as the total number of vascular profiles exhibiting evidence of acute hypertensive injury (fibrinoid necrosis, myointimal proliferation, fragmented internal elastic lamellae, and aneurysmal dilation) expressed per 100 glomeruli to normalize for the amount of renal parenchyma present in individual sections. To examine the quantitative relationships between BP and renal damage, BP parameters were correlated to a composite hypertension-induced renal damage (HIRD) score that was obtained by summing the glomerular and vascular damage scores for each kidney.
**Statistical analysis:** Results are Mean ± SEM. Analysis of variance, followed by Student-Newman-Keuls test or Kruskal-Wallis nonparametric analysis of variance followed by Dunn’s multiple comparison tests was used as appropriate. Linear regression analysis was used to calculate the slopes and intercepts of the BP/HIRD relationship for protocol A studies. Paired t tests or the non-parametric Wilcoxon matched pairs signed-rank tests were used to compare the histologic hypertensive injury in the right kidney (harvested before the initiation of the antihypertensive therapy) to that in the left kidney (harvested after 2-3 weeks of antihypertensive therapy).
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