Hemodynamic basis for the limited renal injury in rats with angiotensin II-induced hypertension

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ANGIOTENSIN II (ANG II) is thought to play a major role in the development and progression of chronic kidney disease (CKD), and its blockade is recommended as a primary strategy for reducing CKD progression (31, 40, 66). It has been postulated that in addition to causing direct hypertensive (barotrauma-mediated) injury, ANG II also activates other blood pressure (BP)-independent tissue injury pathways such as inflammation, oxidative stress, aberrant O2 utilization, hypoxia, and profibrotic signaling (11, 17, 31, 32, 42, 47, 59, 63). Thus, it is widely believed that susceptibility to renal injury is increased in ANG II excess states, and the ANG II infusion model has been extensively used to investigate such mechanisms. However, while the chronic administration of ANG II has been repeatedly shown to produce sustained hypertension and renal injury in rodents (29, 30, 36, 41, 46, 48, 52, 54, 57, 61, 62, 65), such studies have not directly addressed the issue of susceptibility to renal injury, per se, in ANG II-infused animals. Any increase in the physical pressure (i.e., BP) within the intrarenal vasculature, if of sufficient magnitude and regardless of cause, is expected to result in barotrauma and vascular injury (4, 15, 20, 33, 35). Therefore, the susceptibility to hypertensive-induced renal damage (HIRD) in disease states or models can only be directly assessed by an examination of the BP threshold for renal injury and the slope of the relationship between renal injury and BP (i.e., increase in renal injury/mmHg increase in BP) (5, 10). Such quantitative relationships between directly measured BP and HIRD have still not been defined in ANG II-infused models.

Given the plethora of postulated mechanisms of ANG II-mediated renal injury, the degree of renal injury observed in previous studies (29, 30, 36, 41, 46, 48, 52, 54, 57, 61, 62, 65) appears to be surprisingly modest for reasons that remain unclear. Accordingly, the goal of the present study was to define the quantitative relationships between BP and HIRD in ANG II-infused rats and compare it with another very frequently used model of HIRD (2, 3, 22, 56, 58, 70), the Nω-nitro-l-arginine methyl ester (l-NAME)-induced nitric oxide synthesis inhibition model, for which such relationships have been recently defined (2, 3, 22, 56, 58, 70). Given the importance of hemodynamic factors in determining quantitative BP transmission to the renal microvasculature, we also investigated the effects of ANG II versus l-NAME on BP-renal blood flow (RBF) relationships in conscious rats.

METHODS

Animals. All experiments were performed on male Sprague-Dawley rats (Harlan) weighing 250–350 g and fed standard 1% NaCl Purina chow and provided water ad libitum. All animals were cared for in accordance with the Guide for the Care and Use of Laboratory Animals, and all protocols were approved by the Hines Veterans Affairs Institutional Animal Care and Use Committee.

Surgical procedures and experimental design. To investigate the quantitative relationships between BP and HIRD, rats (n = 42) were anesthetized with isoflurane, and a BP radiotransmitter (model TA11PA-C40, Data Sciences, St. Paul, MN) was inserted, via the femoral artery, into the abdominal aorta below the level of the renal arteries for the continuous assessment of BP (sampled for 10 s every 10 min for 24 h/day). After rats had recovered from surgery, baseline

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BP (average of days 5–7 postsurgery), proteinuria (24-h urine collection, sulfosalicylic acid), and serum creatinine levels (colorimetric Quantichrom Creatinine Assay Kit, BioAssay Systems, Hayward, CA) were assessed. One group of rats (n = 23) was then continuously administered L-NAME via drinking water (500 mg/l) for 4 wk. Water intake in male Sprague-Dawley rats from Harlan is ~100 ml/kg·day⁻¹ in our animal facility (22); therefore, the dose of L-NAME in the present study was ~50 mg·kg⁻¹·day⁻¹. Another group of rats (n = 19) was anesthetized with isoflurane, and an osmotic minipump (2ML4, Alzet) was implanted subcutaneously between the scapulae for the chronic administration of either 300 ng·kg⁻¹·day⁻¹ (n = 8) or 500 ng·kg⁻¹·day⁻¹ (n = 11) ANG II. These doses of ANG II and L-NAME were used because they elicit relatively similar increases in BP, as determined from preliminary studies. As there were no significant differences in the BP response or the extent of HIRD between rats administered 300 or 500 ng·kg⁻¹·day⁻¹ ANG II, these data were combined into a single group. A 24-h urine collection was conducted at 2 and 4 wk of hypertension for the determination of proteinuria. At 4 wk, a blood sample was obtained for a final serum creatinine measurement, and kidneys were perfused fixed with paraformaldehyde-lysine-phosphate for the histological assessment of renal injury.

An additional group of male Sprague-Dawley rats from Harlan (n = 15) was chronically instrumented with a BP radiotransmitter and a RBF transducer (model 1RB, Transonic Systems, Ithaca, NY), which was placed on the left renal artery and packed in Dacron mesh to ensure proper alignment of the transducer and vessel (9, 24). The transducer cable was secured to the back muscles, routed subcutaneously, exteriorized at the back of the neck, and connected to a flowmeter (model T106, Transonic Systems) during RBF recordings. Rats recovered for 1 wk after the implantation of the BP transmitter and RBF probe. BP and RBF were then obtained (200 Hz) for 3 h on one to three separate occasions at 24-h intervals in conscious rats. After these baseline BP-RBF measurements, one group of rats (n = 8) was anesthetized and implanted with osmotic minipumps to chronically deliver ANG II (500 ng·kg⁻¹·day⁻¹) for 2 wk, whereas another group (n = 7) was administered L-NAME via drinking water (50 mg·kg⁻¹·day⁻¹) for 2 wk. Three days after the induction of hypertension, BP and RBF recordings were again obtained at 200 Hz for a 3-h period and repeated every 2–3 days for 2 wk.

Assessment of renal injury. Renal injury was assessed in a blinded fashion by one of the investigators (M. Picken) using 4-μm-thick sections stained with periodic acid-Schiff. As previously described (16, 23, 25, 27), glomerular injury was expressed as the total percentage of glomerular surface affected by lesions of either glomerulosclerosis/necrosis and/or ischemic glomerulosclerosis, as previously described (16). We have previously shown that assessment of the severity of glomerular injury using this method compared with a semiquantitative glomerular injury score based on the percentage of glomerular surface involved yields comparable results (26). Tubulointerstitial injury and fibrosis were assessed on a semiquantitative scale of 0–4. The vascular injury score was calculated as the number of interlobular or afferent arterioles exhibiting acute disruptive injury (lesions of necrosis, thrombosis, aneurysmal dilatation, and/or onion skinning) per 100 glomeruli.

Ambient renal hemodynamics. As previously described (22, 55), mean arterial pressure (MAP), renal vascular resistance (RVR), and RBF were averaged for each rat over the two to three separate 3-h recordings at baseline and over the six to seven separate 3-h recordings during ANG II and L-NAME administration.

Time-varying BP-RBF relationships. As previously described (55), each BP and RBF recording was downsampled (20 Hz) and divided into 10-s segments with 50% overlap between successive segments. Average BP and RBF were calculated for each 10-s segment over the entire 3-h recording. The resulting average RBF values for each 10-s segment were associated with a 10-mmHg range (bin) corresponding to the average segment MAP value. The RBF-BP bin data were averaged over the baseline and multiple recordings during ANG II or L-NAME administration for each rat. The RBF-BP bin data at baseline and during ANG II or L-NAME administration were averaged across rats. RBF values are expressed as a percentage of the respective RBF observed when BP was between 100 and 110 mmHg during baseline recordings.

Statistical analysis. Results are means ± SE. Statistical comparisons between groups were performed using two-way repeated-measures ANOVA. A nonparametric Mann-Whitney test was used to evaluate differences in renal injury parameters between groups. Linear regression analysis was used to calculate the slope of the relationship between glomerular injury and BP for each group (increases in glomerular injury/mmHg increases in systolic BP). Analysis of covariance was used to compare the slopes and y-intercepts between groups. One-way repeated-measures ANOVA was used to evaluate time-varying BP-RBF relationships within baseline, ANG II, and L-NAME groups. If necessary, post hoc comparisons were made using a Student-Newman-Keuls test. P values of <0.05 were considered statistically significant.

RESULTS

Body weight, kidney weight, and serum creatinine levels. Baseline body weight and serum creatinine levels were not significantly different between groups (Table 1). Rats administered ANG II gained a significantly greater amount of body weight compared with rats administered L-NAME over the 4-wk protocol. Absolute kidney weight was significantly less in rats administered L-NAME (1.3 ± 0.05 g) versus ANG II (1.6 ± 0.05 g) at the completion of the study; however, no differences were observed when kidney weight was normalized to body weight (Table 1). Final serum creatinine values were significantly greater in the L-NAME versus ANG II model at the completion of the study, suggesting a greater degree of renal impairment (Table 1).

Hypertension and renal injury. The average BP at baseline and during the 4-wk of ANG II (n = 19) and L-NAME (n = 23) administration (presented as 2-day averages) is shown in Fig. 1A. While both ANG II and L-NAME led to sustained increases in BP over the 4-wk protocol, BP was significantly greater between days 4 and 15 in ANG II-infused rats. However, BP levels plateaued in ANG II-infused rats after ~2 wk but continued to rise in L-NAME-infused rats such that significantly higher values were achieved over the last 2 days compared with ANG II-infused rats. The average systolic BP

| Table 1. Body weight, serum creatinine levels, and kidney weight in ANG II- and L-NAME-infused rats |
|----------------------------------------------|-----------------------------------------------|
| **Body Weight, g**                          | **Serum Creatinine, mg/dl**                    |
| **Baseline**                                | **Final**                                     |
| ANG II                                       | 272 ± 5                                       | 332 ± 10 * |
| L-NAME                                       | 265 ± 4                                       | 294 ± 12 * |
| **Baseline**                                | **Final**                                     |
| ANG II                                       | 0.25 ± 0.03                                   | 0.54 ± 0.04 * |
| L-NAME                                       | 0.26 ± 0.03                                   | 0.92 ± 0.07 * |
| **Right Kidney Weight/Body Weight, g/kg**    |                                               |
| ANG II                                       | 4.8 ± 0.1                                     |
| L-NAME                                       | 4.6 ± 0.1                                     |

Values are expressed as means ± SE; n = 19 ANG II (300–500 ng·kg⁻¹·min⁻¹) hypertensive rats and 23 Nω-nitro-L-arginine methyl ester (L-NAME; 50 mg·kg⁻¹·min⁻¹) hypertensive rats. *P < 0.05, maximum vs. baseline; †P < 0.05, maximum vs. ANG II.
ischemic glomerulosclerosis) was significantly higher in L-NAME hypertensive rats. Total glomerular injury (in %), consisting of both glomerulosclerosis/necrosis and ischemic glomerulosclerosis, and tubulointerstitial injury. Total significantly lower average systolic BP in L-NAME versus ANG II hypertensive rats. Moreover, the similar level of proteinuria observed with acute disruptive vascular injury, glomerular injury (sum of glomerulosclerosis/necrosis and ischemic glomerulosclerosis), and tubulointerstitial injury. Total significantly lower average systolic BP in L-NAME versus ANG II-infused rats. Moreover, the similar level of proteinuria observed at 2 wk of hypertension coincided with a significantly lower average systolic BP in L-NAME versus ANG II-infused rats (180 ± 3 vs. 197 ± 1 mmHg, respectively, averaged over days 12–16 of hypertension).

The pattern and magnitude of HIRD in ANG II and L-NAME hypertensive rats are shown in Fig. 2. In both models of hypertension, a pattern of malignant nephrosclerosis was observed with acute disruptive vascular injury, glomerular injury (~75% glomerulosclerosis/necrosis and ~25% ischemic glomerulosclerosis), and tubulointerstitial injury. Total glomerular injury (sum of glomerulosclerosis/necrosis and ischemic glomerulosclerosis) was significantly higher in L-NAME versus ANG II hypertensive rats. While both types of glomerular injury were higher in L-NAME-administered rats, the individual differences did not reach statistical significance.

The magnitude of tubulointerstitial injury paralleled the level of glomerular injury in both models of hypertension and was 2.3-fold greater (P < 0.05) in rats administered L-NAME versus ANG II. In contrast, both the magnitude (average number of vessels exhibiting vascular injury per 100 glomeruli evaluated) and incidence of acute disruptive vascular injury were similar between L-NAME (2.1 ± 0.5, 12 of 23 rats) and ANG II (2.0 ± 0.7, 10 of 19 rats) hypertensive rats. In summary, these data demonstrate a very modest and significantly lower level of glomerular and tubulointerstitial injury in ANG II versus L-NAME hypertensive rats, despite a higher average systolic BP in the ANG II model.

The quantitative relationships between BP and glomerular injury are shown in Fig. 3A. Significant correlations between BP and renal injury were observed in L-NAME (r² = 0.29, P < 0.01) and ANG II (r² = 0.21, P < 0.05) hypertensive rats. The slope of the relationship between BP and renal injury, while higher in rats administered L-NAME (y = 0.31x − 45.21), was not statistically different to that observed in rats administered ANG II (y = 0.19x − 28.88). However, the x-intercept of the relationship between BP and renal injury was significantly higher in ANG II versus L-NAME hypertensive rats, indicating an increased BP threshold for the development of renal injury. The increased BP threshold for hypertensive glomerular injury in ANG II hypertensive rats is also shown in Fig. 3B, which shows the average percent glomerular injury plotted within 10-mmHg systolic BP bins corresponding to the average systolic BP achieved during the duration of hypertension. Similar differences in the threshold for vascular injury were also noted. For example, the average systolic BP of the rats in which vascular injury was observed was 198.3 ± 2.9 mmHg in the ANG II model (10 of 19 rats) and 183.1 ± 3.8 in the L-NAME model (12 of 23 rats). The average systolic BP in rats in which no evidence of vascular injury was found was 183.4 ± 2.6 mmHg in ANG II and 178.1 ± 2.9 mmHg in L-NAME hypertensive rats. Collectively, these data clearly demonstrate a very modest level of HIRD and the higher BP threshold required for the development of such injury in the ANG II versus L-NAME model of hypertension in rats.

Renal hemodynamics in conscious rats administered ANG II and L-NAME. The average MAP, RBF, and calculated RVR obtained from BP-RBF recordings in conscious rats before and during either ANG II (n = 7) or L-NAME (n = 8) administration are shown in Fig. 4. The average BP increase over the 2-wk protocol was significantly greater in rats administered

Fig. 2. Summary of semiquantitative analysis of renal injury in L-NAME and ANG II hypertensive rats. Total glomerular injury (in %), consisting of both glomerulosclerosis (GS)/necrosis and ischemic GS, and tubulointerstitial injury (TI) were greater in L-NAME versus ANG II hypertensive rats. Values are expressed as means ± SE. *P < 0.05 vs. ANG II.

Fig. 1. Blood pressure (BP) and proteinuria at baseline and during chronic administration of Nω-nitro-l-arginine methyl ester (L-NAME) or ANG II. A: radiotelemetrically measured systolic BP at baseline and averaged over 48-h intervals during the 4-wk administration of L-NAME or ANG II. *P < 0.05 vs. L-NAME at the respective time point. B: 24-h proteinuria at baseline and at the second and fourth wk of L-NAME or ANG II. Values are expressed as means ± SE. *P < 0.05 vs. ANG II at 4 wk.
ANG II versus L-NAME (56% vs. 38% increase from baseline, respectively; Fig. 4A), similar to the different BP responses observed during the first 2 wk of ANG II and L-NAME administration in the rats shown in Fig. 1A. However, despite the higher BP, ANG II led to a greater reduction in RBF compared with L-NAME (−41% vs. −23% reduction from baseline, respectively; Fig. 4C). Clearly, this reduction in RBF was due to greater increases in RVR in ANG II versus L-NAME hypertension (171% vs. 82% increase from baseline, respectively; Fig. 4B). Indeed, when BP was between 150 and 180 mmHg during ANG II infusion, RBF was significantly lower than values pre-ANG II values when BP was between 80 and 130 mmHg. Further reductions in RBF were observed during spontaneously fluctuations in which BP exceeded 130 mmHg. Indeed, when BP was between 150 and 180 mmHg during ANG II infusion, RBF was significantly lower than values observed when BP was between 100 and 120 mmHg. In summary, marked differences in BP-RBF patterns were observed in two commonly used models of hypertension associated with renal vasoconstriction. Similar to a recent report from our laboratory (55), these data demonstrate an enhanced renal vasoconstriction response during episodes of spontaneous increases in BP in conscious ANG II-induced hypertensive rats.

**DISCUSSION**

A surprisingly modest degree of renal injury was seen in ANG II-infused rats despite the severe hypertension and presumably activation of the plethora of BP-dependent and BP-independent deleterious mechanisms that have been postulated in ANG II-mediated renal damage (11, 17, 31, 32, 42, 47, 59, 63). Although somewhat counterintuitive, these results are nevertheless consistent with several previous studies that have reported similar modest levels of renal injury in ANG II-infused rodents even with higher levels of NaCl intake than used in the present study (29, 30, 36, 41, 46, 48, 52, 54, 57, 61, 63).
Fig. 5. Effects of L-NAME and ANG II on BP-RBF relationships in conscious chronically instrumented rats. A–D: representative BP-RBF recordings at baseline (A and B) and during L-NAME (C) or ANG II (D). No differences were seen in BP-RBF relationships during baseline recordings in both groups, so these data were averaged. Both L-NAME and ANG II led to significant reductions in RBF (expressed as percent changes from RBF when MAP was within 100–100 mmHg) compared with baseline values (E). However, the pattern of changes in RBF during spontaneous fluctuations in BP was markedly different during ANG II and L-NAME infusion. Whereas L-NAME led to a similar ~25% reduction in RBF across the entire range of BP fluctuations, RBF further decreased during episodes of BP elevations in rats administered ANG II. Values are expressed as means ± SE. *P < 0.05 vs. RBF values when BP was within 100–110 and 110–120 mmHg during ANG II administration.
Indeed, a previous study (54) that compared HIRD in ANG II- versus norepinephrine-infused rats noted that the susceptibility to BP-induced glomerular injury was significantly less in the ANG II model despite the comparable hypertension. However, the apparent discordance between the abundance of postulated mechanisms for ANG II-mediated injury and the relative paucity of observed histological injury has not been directly addressed and the underlying mechanisms have not been investigated.

The significantly higher BP threshold for HIRD and relatively flat slope of the relationship between BP and HIRD in ANG II-infused rats indicate a reduced susceptibility to HIRD compared with rats that receive L-NAME. The primary determinants of such susceptibility to HIRD are expected to be 1) the severity of hypertension, 2) the degree to which the systemic hypertension is transmitted to the renal microvasculature, and 3) the local tissue injury response to a given degree of renal microvasculature BP exposure (5). In this regard, the severity of hypertension was, if anything, greater in the ANG II group (Fig. 1), and there is little evidence to suggest that loss of nitric oxide has more deleterious effects on the local tissue injury response to a given level of BP compared with L-NAME. The primary determinant of such susceptibility to HIRD is most likely to be due to differences in renal hemodynamic factors that govern the degree of renal microvasculature BP transmission. Consistent with such interpretations, the overall greater constriction observed in ANG II-infused rats would be expected to reduce BP transmission and thus barotrauma-mediated injury compared with rats administered L-NAME (5, 8–10, 51). Moreover, in contrast to the relatively stable vasoconstriction observed in rats administered L-NAME, ANG II infusion was associated with a greater variability in BP-RBF relationships with the more severe vasoconstriction occurring during spontaneous BP elevations (21, 45, 53, 55, 64). Such hemodynamic patterns, which we have also recently described with more modest doses of ANG II (125 ng.kg−1.min−1) (55), are expected to provide more effective protection against renal microvasculature transmission of hypertensive episodes and barotrauma-mediated glomerular injury (5, 10). There is also evidence that ANG II may affect more upstream vascular segments (interlobar, arcuate, and interlobular vessels), as demonstrated by the vascular casting study performed by Wilson and Heptinstall (67), which would result in a greater dissipation of the severity of hypertension along the length of the renal vasculature and microvasculature (14, 39, 67). Indeed, as early as 1964, one of the pioneering investigators of hypertensive organ damage, Byrom (13), suggested that the extreme vasoconstriction in upstream renal vascular segments associated with ANG II infusion may protect the more distal vessels by reducing renal BP transmission. The lack of similar renal vasoconstriction observed in conscious rats administered sympathomimetic agents (43, 55) may account for the greater degree of glomerular injury in norepinephrine- versus ANG II-infused rats previously noted (54). It should also be emphasized that a modest, but nevertheless significant, increase in outer medullary tubulointerstitial injury was observed in ANG II- versus norepinephrine-infused rats. While the mechanisms remain to be elucidated, one possibility is that the extensive renal vasoconstriction observed during ANG II infusion may have led to greater levels of ischemia-induced tubulointerstitial injury compared with norepinephrine. Indeed, we have previously suggested that reduced barotrauma-mediated but increased ischemia-mediated renal injury may be a feature of hypertensive models associated with significant renal vasoconstriction (10, 22). Nevertheless, the overall protective importance of renal vasoconstriction is dramatically illustrated by the severe consequences of ANG II infusion in Notch3-deficient mice, which have impaired vasoconstrictor responses (12).

In addition to the ambient tone of the preglomerular vasculature, its ability to appropriately and proportionately respond to BP changes (i.e., RBF autoregulation) is expected to be the other major hemodynamic determinant of BP transmission (5). Recent studies showing that ANG II impairs RBF autoregulation have been interpreted as providing a mechanism for enhancing HIRD in ANG II excess states (29, 30, 36, 38, 50, 61, 65). However, such interpretations are difficult to reconcile with the paucity of renal damage seen in ANG II-infused rats in both the present study and previous studies. An explanation for this apparent discrepancy may relate to the nature of renal autoregulatory impairment that has been observed in the vasoconstricted vasculature of anesthetized ANG II-infused rats and in ex vivo kidney preparations of ANG II-infused rats (29, 30, 36, 38, 50, 52, 65). While these studies indeed demonstrated an impairment of renal autoregulatory function (i.e., a failure of the renal vasculature to respond to changes in BP) after 1 or 2 wk of ANG II infusion in rats, the autoregulatory impairment was manifest as a reduced ability to vasodilate as renal perfusion pressure was lowered. The implications of impaired autoregulation of this nature are completely opposite to impaired autoregulation in a vasodilated renal vasculature that fails to appropriately vasoconstrict when renal perfusion pressure increases (e.g., the remnant kidney). Whereas the latter impairment increases the susceptibility to barotrauma-mediated injury, the former impairment would be expected to reduce microvascular BP transmission and possibly increase the susceptibility to ischemia-mediated injury (5, 10, 51, 55).

Ambient efferent arteriolar resistance is an additional hemodynamic factor that may impact the severity of glomerular hypertension and injury in hypertensive models. While both ANG II and L-NAME (3, 18, 49) are known to cause efferent vasoconstriction, ANG II is thought to be a more selective and potent efferent vasoconstrictor and would have been expected to cause greater glomerular hypertension and injury. The rather modest levels of glomerular injury actually observed in ANG II-infused rats is accordingly more consistent with a greater vasoconstrictive effect on the preglomerular vasculature, at least in the exogenously infused ANG II model, as has indeed been shown by a large number of laboratories (18, 34, 37, 44, 50). The significantly lower level of proteinuria, a robust marker of glomerular capillary pressure (69), observed in ANG II versus L-NAME hypertensive rats at 4 wk is also consistent with a greater preglomerular vasoconstrictor effect.

The dominant role played by preglomerular tone and autoregulatory ability in determining the pattern and severity of HIRD is also evident when the ANG II model is compared with the 5/6 renal ablation model. The preglomerular vasodilatation and impaired autoregulatory ability characteristic of this model result in a greatly reduced BP threshold for HIRD (~125 mmHg) and a much steeper slope of the relationship between BP and HIRD (6, 7, 25–27). However, perhaps a more relevant comparison is with another model of HIRD with intact renal...
mass, the salt-supplemented stroke-prone spontaneously hypertensive rat. More modest levels of renal injury as well as a smaller slopes of the relationship between BP and HIRD were observed in ANG II, as well as L-NAME, hypertensive rats (slope: 0.19 ± 0.09 and 0.31 ± 0.11 change in renal injury/change in mmHg, respectively) compared with that recently reported in salt-supplemented stroke-prone spontaneously hypertensive rats with a similar duration and magnitude of hypertension (slope: 1.2 ± 0.2 change in renal injury/change in mmHg) (28). This differential susceptibility to HIRD may also be explained by differences in ambient renal vascular tone (10, 45) given that renal vasoconstriction, similar to that observed in rats administered ANG II and L-NAME, is not observed in salt-supplemented stroke-prone spontaneously hypertensive rats (1).

The morphological pattern of HIRD observed in the present study provides additional insights regarding the pathogenesis of such injury (5, 28). We have suggested that a malignant nephrosclerosis pattern of HIRD, as seen in the present study, supports a barotrauma-mediated pathogenesis and develops when the magnitude of hypertension exceeds both the vascular threshold for acute disruptive injury and autoregulatory capacity to protect glomerular capillaries (5, 8, 23, 28). The evidence that the most severe cases of HIRD were observed primarily in those rats whose average 4-wk systolic BP exceeded theity to protect glomerular capillaries (5, 8, 23, 28). The evidence supports a barotrauma-mediated pathogenesis and develops nephrosclerosis pattern of HIRD, as seen in the present study, of such injury (5, 28). We have suggested that a malignant hypertension (slope: 0.19 ± 0.09 and 0.31 ± 0.11 change in renal injury/change in mmHg, respectively) compared with that recently reported in salt-supplemented stroke-prone spontaneously hypertensive rats with a similar duration and magnitude of hypertension (slope: 1.2 ± 0.2 change in renal injury/change in mmHg) (28). This differential susceptibility to HIRD may also be explained by differences in ambient renal vascular tone (10, 45) given that renal vasoconstriction, similar to that observed in rats administered ANG II and L-NAME, is not observed in salt-supplemented stroke-prone spontaneously hypertensive rats (1).

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Finally, these data strongly suggest that the extensive use of chronic ANG II infusion as a model to investigate the pathogenesis of progressive renal damage may not be merited due to the dominant and protective preglomerular vasoconstriction observed in such models. Yet, it is of note that ANG II infusion is the most commonly used model of hypertension in research grants sponsored by the Vascular Biology and Hypertension Branch within the National Heart, Lung, and Blood Institute of the National Institutes of Health (19). In this context, it may also be important to note that the phenotype of renal injury observed after chronic infusion of pharmacological doses of ANG II is different from that seen in most states of CKD progression in humans, which are characterized by progressive glomerulosclerosis and normal, or only mildly elevated renin levels. Accordingly, the BP-independent deleterious effects of ANG II in CKD states have been attributed to local renin-angiotensin system activation in renal tissues (31, 42, 50, 59, 60, 68). Regardless of the merits of the claims of BP independence in such studies (5, 6, 10, 23, 26), the ANG II infusion model does not seem to be representative of CKD states. However, it does provide a demonstration of the predominant qualitative importance of physical BP transmission in the pathogenesis of HIRD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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