Blood pressure-renal blood flow relationships in conscious angiotensin II- and phenylephrine-infused rats

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Polichnowski AJ, Griffin KA, Long J, Williamson GA, Bidani AK. Blood pressure-renal blood flow relationships in conscious angiotensin II- and phenylephrine-infused rats. Am J Physiol Renal Physiol 305: F1074–F1084, 2013. First published July 3, 2013; doi:10.1152/ajprenal.00111.2013.—Chronic ANG II infusion in rodents is widely used as an experimental model of hypertension, yet very limited data are available describing the resulting blood pressure-renal blood flow (BP-RBF) relationships in conscious rats. Accord-ingly, male Sprague-Dawley rats (n = 19) were instrumented for chronic measurements of BP (radiotelemetry) and RBF (Transonic Systems, Ithaca, NY). One week later, two or three separate 2-h recordings of BP and RBF were obtained in conscious rats at 24-h intervals, in addition to separate 24-h BP recordings. Rats were then administered either ANG II (n = 11, 125 ng·kg⁻¹·min⁻¹) or phenylephrine (PE; n = 8, 50 mg·kg⁻¹·day⁻¹) as a control, ANG II-independent, pressor agent. Three days later the BP-RBF and 24-h BP recordings were repeated over several days. Despite similar increases in BP, PE led to significantly greater BP lability at the heart beat and very low frequency bandwidths. Conversely, ANG II, but not PE, caused significant renal vasoconstriction (a 62% increase in renal vascular resistance and a 21% decrease in RBF) and increased variability in BP-RBF relationships. Transfer function analysis of BP (input) and RBF (output) were consistent with a significant potentiation of the renal myogenic mechanism during ANG II administration, likely contributing, in part, to the exaggerated reductions in RBF during periods of BP elevations. We conclude that relatively equipres-sor doses of ANG II and PE lead to greatly different ambient BP profiles and effects on the renal vasculature when assessed in conscious rats. These data may have important implications regarding the pathogenesis of hypertension-induced injury in these models of hypertension; hemodynamics; blood pressure variability.

INCREASED ACTIVITY OF the renin-angiotensin-aldosterone system (RAAS) (40, 56, 73) is postulated to be a major contributor to chronic kidney disease progression through both blood pressure (BP)-dependent and -independent mechanisms (7, 28, 39, 73). Accordingly, chronic ANG II infusion is extensively used to investigate mechanisms that mediate renal damage in hypertensive states characterized by enhanced RAAS activation (3, 20, 42, 65, 71). Renal parenchymal injury with significant tubulointerstitial fibrosis and a propensity to develop salt-sensitive hypertension has been observed after ANG II infusions (44, 57). Both barotrauma and renal vasoconstriction-mediated tissue ischemia have been postulated to initiate the pathogenic cascades that lead to renal injury after chronic ANG II infusions. However, despite its wide use, there is a paucity of experimental data describing the BP-renal blood flow (RBF) relationships in conscious ANG II-infused animals, and the relative contribution of these two initiating mechanisms has remained uncertain and controversial. Most of the renal vascular responses to ANG II have been investigated in terms of steady-state relationships and usually in anesthetized animals. Although such data have undoubtedly provided important insights into the directional changes, they nevertheless have significant limitations given the effects of anesthesia on RBF (23, 82) and the associated abrogation of the considerable time-dependent variability in BP-RBF relationships that is normally observed in conscious rats (23, 58, 69, 81). Thus, the effects of ANG II on such time-dependent variability in BP-RBF relationships remain unknown. The present studies were performed to examine the effects of continuous infusion of ANG II on ambient BP and RBF profiles, as well as the variability of BP-RBF relationships in the presence of modest increases in BP. As phenylephrine (PE) administration has also been reported to have similar effects on BP and renal injury in rats (18, 43), experiments were also performed in conscious rats continuously administered PE to evaluate the effects of an ANG II-independent pressor agent on such BP and renal hemodynamic profiles.

MATERIALS AND METHODS

Animals. All experiments were performed on male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 250–350 g and fed a standard 1% NaCl Purina chow (Purina no. 5008) 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 VA Institutional Animal Care and Use Committee.

Surgical procedures. Rats were anesthetized with pentobarbital sodium (50 mg/kg ip) anesthesia, and all surgeries were performed on a temperature-controlled warming board using aseptic techniques. During the initial surgery, a BP radiotransmitter (model TA11PA-C40; Data Sciences, St. Paul, MN) was inserted, via the femoral artery, into the abdominal aorta just below the level of the renal arteries and a RBF transducer (model 1RB; Transonic Systems) was placed around the left renal artery and packed in Dacron mesh to ensure proper alignment of the transducer and vessel (8, 29). The transducer cable was secured to the back muscles, routed subcutaneous-ly, exteriorized at the back of the neck, and connected to a flowmeter (model T106; Transonic Systems) during RBF recordings. ANG II and PE were purchased from Sigma and administered via the implantation of osmotic minipumps (Durect, Cupertino, CA) positioned subcutaneously between the scapulae.

Experimental design. Rats were allowed to recover for 1 wk following the implantation of the BP transmitter and RBF probe. In conscious rats, BP and RBF were then obtained for 2 h at a sampling rate of 200 Hz on 1–3 separate occasions at 24-h intervals. In addition to these simultaneous BP and RBF recordings, BP was separately sampled at 200 Hz or 2 times for 24 h for analysis of ambient BP...
profiles and BP power spectra. Following baseline BP-RBF measurements, rats were anesthetized and implanted with osmotic minipumps to chronically deliver either ANG II (125 ng·kg\(^{-1}\)·min\(^{-1}\); \(n = 11\)) or PE (50 mg·kg\(^{-1}\)·day\(^{-1}\); \(n = 8\)) for 1 wk, doses that elicited modest increases in BP in normal-salt diet-fed rats (32, 43). Starting ~48 to 72 h later, 1–3 simultaneous BP and RBF recordings were again obtained at 200 Hz for a 2-h period. Similar to baseline measurements, BP was separately sampled at 200 Hz on 1–2 separate occasions for 24 h to examine the effects of ANG II and PE on ambient BP profiles and on BP power spectra. Twenty-four-hour BP recordings were made in 7 of the 11 rats administered ANG II, and in all of the rats administered PE.

Ambient heart rate and BP load profiles. The effect of ANG II and PE on heart rate and BP load was estimated using power spectral analysis. The total BP load or power (energy/unit time) can be separated into two major components consisting of its mean value [direct current (DC) BP power] and that because of its fluctuations from the mean because of heart beat and other slower neurohumoral mechanisms [alternating current (AC) BP power] (6, 8, 9). Accordingly, individual 24-h BP recordings (200 Hz) were resampled to 20 Hz after being low pass filtered to remove signal components with frequencies greater than 10 Hz. The recording was then divided into ~100 segments of 32,768 samples with 50% overlap of segments. The BP power spectra were determined using Welch’s averaged periodogram method with a fast Fourier transform applied to each 100 segments of 32,768 samples with 50% overlap of segments. The BP power spectra were determined using Welch’s averaged periodogram method with a fast Fourier transform applied to each segment after linear detrending and multiplication by a Hanning

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Table 1. Twenty-four-hour HR, MAP, and BP power distribution in ANG II- and PE-infused rats

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<tr>
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<th>BP Power, mmHg²</th>
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<tr>
<td></td>
<td>VLF 0.0006–0.1 Hz</td>
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<tr>
<td>HR, bpm</td>
<td>18 ± 1</td>
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<td>MAP, mmHg</td>
<td>31 ± 5</td>
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<tr>
<td>Baseline</td>
<td>23 ± 3</td>
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<td>BP, mmHg</td>
<td>97 ± 16*†</td>
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ANOVA effects

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<th>ANG II vs. PE</th>
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<tr>
<td>Baseline vs. drug</td>
<td>P &lt; 0.001</td>
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<td>ANG II vs. PE</td>
<td>P &lt; 0.005</td>
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<td>Interaction</td>
<td>P &lt; 0.005</td>
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Values are expressed as means ± SE. ANG II (n = 7; 125 ng·kg⁻¹·min⁻¹), phenylephrine (PE; n = 8; 50 mg·kg⁻¹·day⁻¹). HR, heart rate; MAP, mean arterial pressure; BP, blood pressure; VLF, very low frequency; LF, low frequency; HF, high frequency; NS, not significant. *P < 0.05 vs. baseline. †P < 0.05 vs. ANG II.

BP power), it had a more potent effect on AC BP power compared with ANG II.

**Ambient renal hemodynamics in ANG II- and PE-infused rats.** The average MAP, RVR, and RBF obtained from the simultaneous BP-RBF recordings (~2 h) are presented in Fig. 2. ANG II and PE led to a statistically similar 28% and 19% increase in MAP, respectively; however, significant differences were noted in the RVR and RBF responses. Whereas RVR and RBF were not significantly altered during PE, ANG II led to a 62% increase in RVR (P < 0.05) and 21% decrease in RBF (P < 0.05) compared with baseline values. These data indicate that ANG II is a more potent renal vasoconstrictor in conscious rats compared with PE at similar pressor doses.

**Ambient pulse pressure and renal pulse flow in ANG II- and PE-infused rats.** To gain additional insights into the effects of ANG II and PE on the renal vasculature, the changes in pulsatility of BP and RBF were evaluated (Fig. 3). As shown in Fig. 3, A and B, striking differences were noted between ANG II and PE with respect to both pulse pressure and pulse flow. PE led to a robust 46% increase in pulse pressure (P < 0.05) and 41% increase in pulse flow (P < 0.05). Conversely, ANG II led to a very modest 7% increase in pulse pressure (NS) but a significant 35% decrease in pulse flow (P < 0.05). Such data provide further evidence indicating significant differences with respect to the effects of ANG II and PE on the renal vasculature.

**Time-varying BP-RBF relationships in conscious ANG II- and PE-infused rats.** Fig. 4 shows the results of the BP-RBF segment analysis at baseline and during ANG II and PE infusion in conscious rats. Because no significant differences in the BP-RBF relationships were observed at baseline between ANG II and PE groups, these data have been averaged between groups for presentation clarity in Fig. 4E, which shows the BP-RBF analysis for 10-s segments and 10-mmHg BP bins. Similar patterns of BP-RBF relationships were observed regardless of the length of the time window (1–100 s) or width of the BP bin (5–20 mmHg) (data not shown). During baseline recordings, RBF was well preserved over the smaller range of BP fluctuations (representative images shown in Fig. 4, A and B), although a modest, but significant, 9% decrease in RBF was observed during periods of BP elevations (110–120 mmHg) compared with RBF when BP was within baseline levels (90–100 mmHg). During ANG II and PE administration, there was considerable time-dependent variability in the BP-RBF relationships observed between animals, on different days in the same animal, and even more strikingly within a single data record of an individual animal. Although the time-dependent variability in BP was considerably exaggerated by both PE and ANG II, the pattern of associated RBF changes was very different. In the case of PE, RBF was largely similar across a wide range of spontaneous changes in BP (Fig. 4E with representative image shown in Fig. 4D). Conversely, RBF exhibited significant reductions during periods of BP increases in ANG II-infused rats (Fig. 4E with representative image shown in Fig. 4C). In summary, the BP-RBF bin analysis demonstrates that chronic ANG II infusion is associated with exaggerated renal vasoconstriction during episodes of spontaneous BP increases.

**Transfer functions in conscious ANG II- and PE-infused rats.** Transfer function analyses between fluctuations in BP (input) and RBF (output) from the 2-h BP-RBF recordings are summarized in Table 2. No significant differences in any component of the transfer functions were detected at baseline between ANG II and PE groups; therefore, these data have been averaged between groups for presentation clarity (Fig. 5).

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**BP-RBF RELATIONSHIPS IN CONSCIOUS ANG II- AND PE-INFUSED RATS**

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![Fig. 1. Computed 24-h ambient blood pressure (BP) power spectral density (PSD, (mmHg²)/Hz) at baseline (n = 15) and during ANG II (ANG II; n = 7) and phenylephrine (PE; n = 8) administration. Because no significant differences were observed with respect to the BP PSD obtained during baseline recordings, these data have been averaged between groups for presentation clarity. Significant differences in the effects of ANG II and PE were observed at several different frequency ranges of the 24 h. BP spectra (see Table 1 for details).**
We have previously suggested that the use of such transfer function analysis has limitations with respect to the assessment of autoregulatory capacity; however, it may allow one to investigate the effects of various hormonal and/or neural inputs on the operational characteristics of the two major components of autoregulation, the TGF, and the myogenic response (2, 8, 29). Significant effects were noted with respect to the myogenic mechanism. The only directionally similar effect elicited by ANG II and PE was an increase in the operating frequency of the myogenic mechanism, as evidenced by a rightward shift in the signature resonance peak of the myogenic mechanism (Fig. 5D). ANG II also led to a significant decrease in the coherence at 0.05–0.1 Hz (Fig. 5B), again indicating enhanced buffering of renal microvascular pressure transmission. Conversely, PE led to a significant reduction in the fractional gain of the signature resonance peak of the myogenic mechanism (Fig. 5D). Furthermore, directionally opposite changes compared with ANG II were observed in the phase peak (Fig. 5C) and slope-of-gain reduction (Fig. 5D) with minimal changes observed in the coherence at 0.05–0.1 Hz (Fig. 5B). These changes are consistent with a reduced buffering of systemic BP fluctuations to the renal vasculature during PE administration compared with baseline (26). The only significant change observed with respect to the TGF response was the directionally opposite effects of ANG II to attenuate and PE to potentiate the fractional gain of the TGF signature resonance peak. In summary, the transfer function analysis suggests that ANG II enhances the myogenic response of the renal microvasculature to oscillations of BP, whereas such changes were not observed during PE at the doses administered.

DISCUSSION

The precise pathogenesis of renal damage in hypertensive states, including those characterized by an increased activity of RAAS, continues to be the subject of ongoing investigations. The present studies in conscious chronically instrumented rats provide...
Fig. 4. Effects of ANG II and PE on BP-RBF relationships in conscious chronically instrumented rats. Representative BP-RBF recordings at baseline (A and B) and during ANG II (C) or PE (D). When expressed as % change from RBF when BP was within 90–100 mmHg (E), only ANG II led to marked reductions in RBF during episodes of BP elevations. No differences were seen in BP-RBF relationships during baseline recordings in both groups so these data have been averaged. Values are expressed as means ± SE. *P < 0.05 vs. respective RBF at baseline BP (90–100 mmHg). #P < 0.05 vs. respective RBF at 100–110- and 110–120-mmHg BP bins. ^P < 0.05 vs. respective RBF at 100–110-, 110–120- and 120–140-mmHg BP bins. †P < 0.05 vs. respective RBF at 100–110-, 110–120-, 120–130-, and 130–140-mmHg BP bins.
new insights and demonstrate marked differences in the ambient BP, renal hemodynamic, and BP-RBF relationship response to modestly pressor doses of ANG II and PE. Such data may have considerable pathophysiological implications for the investigation of mechanisms of hypertension-induced renal injury.

**Ambient BP profiles.** Although the pathogenic significance of BP variability patterns remains controversial (25, 35, 60, 74), striking differences were observed in 24-h ambient BP profiles in ANG II vs. PE-infused animals. Whereas ANG II led to more robust increases in the average 24-h BP (DC BP Power), PE resulted in significantly greater BP lability (AC BP power), which was primarily manifested within two frequency bandwidths: 1) BP fluctuations due to the heart beat (~6 Hz) and 2) the slower BP fluctuations occurring within the VLF band (~0.1 Hz). Increased amplitude of BP fluctuations at the heart beat frequency (i.e., pulse pressure) is largely dependent on stroke volume and arterial compliance (4, 50). Because PE is a selective α1-adrenergic antagonist with minimal direct cardiac effects, the PE-induced amplification of pulse pressure was most likely mediated by a reduced arterial compliance (17, 55). This is consistent with the association between increased arteriolar stiffness (i.e., reduced compliance) and pulse pressure amplification that is observed with aging (63).

The most dramatic increase in AC BP power in PE-infused rats was observed within the VLF bandwidth. Compared with the more frequently investigated and better understood origin of the LF and HF ranges of BP variability, the potential sources of BP variability within the VLF range are only beginning to emerge. A recent study by Radaelli et al. (72) reported that α2 adrenergic receptors contribute to VLF BP oscillations via activation of L-type Ca2+ and Ba2+-sensitive K+ channels. A subsequent study by Langager et al. (53) similarly reported a role of sympathetically mediated activation of L-type Ca2+ channels in the generation of VLF BP oscillations. Conversely, the increased VLF BP variability observed in PE-infused rats could have resulted from a reduction in BP buffering. For example, previous studies have reported an increase in VLF BP oscillations following baroreflex denervation (46, 49). Administration of PE may be analogous to baroreflex denervation in that baroreflex-mediated changes in peripheral vascular resistance may be largely attenuated because of the chronic stimulation of α1-adrenergic receptors. Other factors have also been reported to modulate VLF BP oscillations, including the RAAS and nitric oxide (15, 22). To this extent, our data are also in agreement with these previous studies, as evidenced by the ANG II-induced increase in VLF BP power, although to a significantly lesser extent compared with PE-infused rats. Contrary to the effects of PE on BP oscillations within the VLF range, PE administration led to a decrease in the amplitude of oscillations within the LF range (0.1–1 Hz); whereas ANG II increased the magnitude of such BP oscillations. The reasons remain to be defined (45, 54); however, vascular myogenic responses have been implicated in the generation and buffering of LF BP fluctuations (1, 24, 60, 66). Of particular relevance, parallel differences between ANG II and PE were observed with respect to the fractional gain of the myogenic response in the renal transfer function data (see Table 2).

**Ambient renal hemodynamics.** In the present study, continuous ANG II administration led to sustained reductions in RBF measured over several days. Although the acute renal vasoconstrictive effects of ANG II have been extensively documented in rodents, previous studies at single time points after chronic ANG II infusion have failed to show significant RBF reductions in anesthetized or conscious rats, possibly because of the counteracting effects of increased perfusion pressure (67, 68, 83). Brands et al. (13), however, recently reported a reduction of RBF measured over several days in conscious ANG II-infused mice, although the dose of ANG II required to elicit such RBF responses was significantly higher than that administered to rats in the present study, and the effects on time-dependent variability in BP-RBF relationships were not reported. In any event, given the spontaneous and often large fluctuations of arterial BP and RBF that were found in the present study, acute single assessments of hemodynamics may not be sufficient to fully characterize the chronic effects of ANG II on RBF.

In contrast to ANG II-infused rats, RBF was unchanged from baseline levels during PE infusion. Although the renal vasoconstrictive effects of catecholamines are well documented (38, 48), there is evidence that the effects of adrenergic agents on renal vascular function are dependent on the dose, route of administration, and the state of the animal during investigation. For instance, Kleinjans et al. (52) demonstrated drastic reductions in glomerular filtration rate (GFR) and RBF during intrarenal infusion of high doses of norepinephrine (NE) in anesthetized but not conscious rats (52). Furthermore, intrarenal NE administration has been used to produce ischemic acute renal failure in anesthetized animals (14, 16). By contrast, increases in RBF were observed during acute intravenous and intrarenal administration of NE in conscious dogs (5). Although PE, unlike NE, acts mainly on the α-adrenergic

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<th>Fractional Gain</th>
<th>Coherence at 0.05-0.1 Hz</th>
<th>Slope of Gain Reduction, db/decade</th>
<th>ANOVA effects</th>
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<tr>
<td>Baseline</td>
<td>0.23 ± 0.01</td>
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<td>P &lt; 0.005</td>
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<tr>
<td>ANG II</td>
<td>0.27 ± 0.01</td>
<td>3.0 ± 0.2*</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline</td>
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<td>P &lt; 0.005</td>
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<tr>
<td>PE</td>
<td>0.25 ± 0.01</td>
<td>1.6 ± 0.1†</td>
<td>NS</td>
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*Values are expressed as means ± SE. ANG II (n = 10; 125 ng·kg−1·min−1), PE (n = 8; 50 mg·kg−1·day−1). TGF, tubuloglomerular feedback; NS, not significant. *P < 0.05 vs. baseline. †P < 0.05 vs. ANG II.
receptors, the lack of reduction in RBF during PE administration in the present studies is consistent with such observations. Similarly, adrenergic agents, including PE, in appropriate doses have been used clinically to support BP without compromising RBF and renal function (21). Differential renal vascular responses to ANG II and NE have also been observed in humans (78).

**Ambient pulse pressure and renal pulse flow.** The increase in renal pulse flow during PE was likely a secondary consequence of the PE-induced increase in pulse pressure, given there were no significant effects of PE on RBF (an important determinant of renal pulse flow). The decrease in pulse flow in ANG II-infused rats, thus, likely stemmed from the significant reduction in RBF. These data suggest that modification of vascular compliance may be an important target of sympathetically mediated \( \alpha_1 \)-adrenergic stimulation. This observation is in agreement with previous studies that have found sympathetically mediated changes in vascular compliance, independent of diameter, in conduit vessels (11, 61, 76, 86). Alternatively, the greater reduction in HR observed in PE-vs. ANG II-infused rats could have contributed, in part, to parallel differences in stroke volume and, thus, pulse pressure.

**Time-dependent variability in BP-RBF relationships.** A striking time-associated variability of RBF was observed at any given BP in individual rats in the present study, which has also been observed previously (58, 70, 81). Nevertheless, despite this variability in RBF, the BP-RBF bin analysis in the present study (Fig. 4E) and in the previous study of Pires et al. (69) revealed an overall constancy of average RBF over the autoregulatory range of pressures not only during single recordings but over several days as well. Such a pattern observed at baseline and even after PE is consistent with the concept of a successful achievement of overall RBF autoregulation. However, when the beat-to-beat BP-RBF relationships are examined, Skarlatos et al. (81) reported that an autoregulatory like
Pattern was observed, at the most, 35% of the time. Qualitatively similar BP-RBF patterns were observed when segments of 10 or 100 s were used, as also noted in our analyses. Likewise, Pires et al. (70) concluded that an autoregulatory-like pattern of spontaneous BP-RBF relationships could not be modeled in normal, sinoaortic baroreceptor- innervated rats using 1-s segment lengths and 2.5-mmHg BP bins. In a similar manner, we have previously noted that assessment of dynamic autoregulation in conscious rats with intact or reduced renal mass yields estimates that are significantly lower than those obtained during steady-state autoregulatory studies (8). We have, therefore, suggested that such spontaneous fluctuations in RBF represent the composite responses to various neurohumoral inputs at multiple frequencies, thus making it difficult to separate, define, and quantify autoregulatory responses in conscious rats (8, 58). Similar concerns were noted by Skarlatos et al. (81). We have additionally suggested that while autoregulatory responses to BP changes provide one mechanism for stabilization of RBF, there are likely other mechanisms that may also mediate an overall stability and set point regulation of RBF independent of autoregulatory responses (58). These inferences were based on the lack of differences in ambient RBF and GFR in 5/6 ablated rats despite large differences in BP and autoregulatory capacity (31, 58). We had also noted that in the absence of such compensatory set point regulation, antihypertensive therapy in individuals with autoregulatory impairment would not be feasible and would result in acute renal hyperperfusion and declines in GFR (58). The identity of such mechanisms remains to be identified, but it seems to be intimately related to body surface area and metabolic needs (30).

Given these considerations, the striking progressive and consistent reductions in RBF with increasing BP in ANG II-infused rats indicates qualitative and/or quantitative differences in the interactions between various factors that influence time-associated RBF variability in these rats vs. PE-infused rats. For example, it is possible that increases in sympathetic activity may be contributing to the episodes of exaggerated RBF responses during BP elevations in ANG II-infused rats (19, 59, 87). A similar mechanism may be responsible for the small, but significant, decreases in RBF observed during BP elevations in control rats. Conversely, the absence of such a pattern in the PE-infused rats may be due to a reduction of baro reflex input due to constant \( \alpha_1 \)-adrenergic stimulation. However, it is also possible that the interaction between ANG II and the myogenic response triggered by increasing BP results in an exaggerated and dysregulated vasconstriction (34, 41, 81). Such observations are consistent with the previously described enhancement of myogenic activity by ANG II (36, 51, 62). In contrast, others have reported reduced autoregulatory responses in the vasoconstricted renal vasculature of anesthetized ANG II-infused rats (33, 37, 83). However, it is possible that additional interactions may occur under anesthesia and not be replicative of the responses in conscious animals. Of particular relevance, the implications of impaired autoregulation for renal microvasculature BP transmission and tissue injury are directionally opposite in a vasoconstricted (i.e., ANG II) vs. a vasodilated (i.e., remnant kidney) vasculature (7, 10). Further support for our interpretations of the interaction with ANG II and the myogenic response comes from the transfer function data obtained during dynamic autoregulation studies.

**Transfer functions.** Significant changes in transfer functions were observed with both ANG II and PE. The most robust effects were seen on the myogenic response. Directionally opposite effects of ANG II and PE were observed on the myogenic resonance peak with ANG II potentiating and PE attenuating it. These changes were paralleled by significant changes in phase peak, coherence, and slope-of-gain reduction. Just et al. (47) similarly reported a significant potentiation of the myogenic resonance peak during ANG II infusion in conscious dogs. These effects of ANG II on the myogenic mechanism are consistent with the observed pattern of the BP-RBF relationships that we observed. The disproportionate and exaggerated reductions in RBF during acute BP elevations indicate a possible dysregulated and ANG II-sensitized myogenic mechanism. The underlying cellular mechanisms by which ANG II potentiates renal myogenic activity have been previously described and include the modulation of PKC (51) and G protein-coupled receptor (36, 62) pathways. By contrast, the cellular mechanisms responsible for the apparently reduced myogenic responses after PE remain to be elucidated. In contrast to the myogenic response noted in the conscious rat (present studies) and in the conscious dog (47), Saed et al. (75) observed a reduced slope of gain reduction and diminished phase peak in anesthetized rats following 2 wk of ANG II at a higher dose (250 ng kg\(^{-1}\) min\(^{-1}\)) than used in the present study. These effects were further exaggerated in ANG II-infused rats fed a high-sodium diet (4% NaCl). The reasons for such differences remain to be defined but may involve the differences in dosage and duration of ANG II, dietary salt intake, and the potential effects of anesthesia.

Both ANG II and PE administration led to a significant increase in the operating frequency of the myogenic mechanism. Just et al. (47) did not observe a significant effect of ANG II on the operating frequency of the myogenic mechanism in conscious, resting dogs. While the reasons for such differences between studies are not readily apparent, some potential explanations include acute vs. chronic ANG II administration, differences in the level of BP achieved during ANG II, as well as species differences. However, an enhanced myogenic response during nitric oxide synthase (NOS) blockade has previously been reported (84). Furthermore, a subsequent study demonstrated that perfusion pressure directly modulates the frequency response of the myogenic mechanism and that the increased operating frequency of the myogenic mechanism observed during NOS inhibition was a consequence of the concurrent elevation in BP (85). This provides a potential mechanism, whereby both ANG II and PE can increase the operating frequency of myogenic mechanism, as shown in the present study, although future studies are required to validate such pressure-induced pathways, as well as the underlying mechanisms.

The observed effects of ANG II and PE on the TGF mechanism in the present study are at some variance to previous results. In contrast to the attenuation of the TGF resonance peak by ANG II, Just et al. (47) noted a trend for ANG II to enhance and angiotensin-converting enzyme inhibition to attenuate the TGF resonance peak, although statistical significance was not achieved. Similarly, an enhancement of TGF responses by ANG II has been noted during micropuncture studies (12, 64, 79). The mechanisms responsible for such differences remain to be defined. Similarly, in contrast to the
significant enhancement of the TGF resonance peak by PE in the present study in conscious rats, no effects were seen during intravenous or intrarenal PE administration in anesthetized rats (80). Such effects of PE on the TGF resonance peak are consistent with either an enhancement in gain or a reduction in the damping of the TGF response and will require future studies to elucidate the underlying mechanisms.

In summary, the present studies demonstrate substantial differences in the ambient BP profiles and renal vascular responses at comparable pressor doses of ANG II and PE. The renal vascular effects of ANG II in conscious rats in the present study indicate a potential attenuation of intrarenal BP transmission, thereby counteracting its BP-independent deleterious effects. These results are consistent with previous studies reporting a very modest degree of hypertensive glomerular injury in chronic ANG II-infused rodents (42, 65, 71, 77). Future studies investigating the quantitative relationships between chronic radiotelemetrically measured BP and renal damage will be needed to validate these insights.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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