Renal Sympathetic Neuroeffector Function in Renovascular and Angiotensin II–Dependent Hypertension in Rabbits

Sandra L. Burke, Geoffrey A. Head, Gavin W. Lambert, Roger G. Evans

Abstract—We tested the hypotheses that the gains of specific renal sympathetic neuroeffector mechanisms are altered in secondary hypertension and that the nature of these alterations depends on the precise experimental setting of the kidney. Rabbits were sham operated, or made comparably hypertensive (mean arterial pressure increased 17% to 24%) by clipping the left or right renal artery or by chronic infusion of angiotensin II (20 to 50 ng kg\(^{-1}\) min\(^{-1}\) SC). Four to 6 weeks later, under pentobarbital anesthesia, the left renal nerves were sectioned and electrically stimulated at low (0 to 2 Hz) and high (4 to 8 Hz) frequencies. Neurally evoked reductions in total renal blood flow, cortical perfusion, urine flow, and sodium excretion and increases in renal norepinephrine spillover were not significantly greater in kidneys of hypertensive rabbits than normotensive controls. Neurally evoked increases in renal renin release and the slope of the relationship between renin release and norepinephrine spillover were less in kidneys of hypertensive rabbits than normotensive controls. Low-frequency renal nerve stimulation reduced medullary perfusion, which was negatively correlated with renal norepinephrine spillover in kidneys from all 3 groups of hypertensive rabbits but not normotensive controls. Two-hertz stimulation reduced medullary perfusion by 19% in hypertensive rabbits but not in normotensive rabbits. Thus, of all of the renal sympathetic neuroeffector mechanisms studied, only neural control of medullary perfusion was enhanced in these models of secondary hypertension. This effect appears to be mediated postjunctionally, not through enhanced neural norepinephrine release, and may contribute to the development and/or maintenance of hypertension in these models. (Hypertension. 2007;49:932–938.)

Key Words: kidney circulation ■ renal medulla ■ renal sympathetic nerves ■ renin–angiotensin system ■ sodium excretion

The renal sympathetic nerves appear to contribute to the pathogenesis of essential hypertension. Human essential hypertension is accompanied by increased sympathetic nerve activity, including to the kidney, and defects in neuronal norepinephrine uptake. Renal sympathetic nerve activity (RSNA) is greater in spontaneously hypertensive rats than in normotensive rats, and renal denervation delays or blunts the development of hypertension in spontaneously hypertensive rats. The role of the sympathetic nervous system in secondary hypertension remains controversial. Sympathetic vasmotor drive may be increased in hypertension induced by chronic infusion of angiotensin II (Ang II; Ang II–induced hypertension) and in 2 kidney, 1 clip (2K1C) hypertension because depressor responses to sympathetic stimulation or ganglionic blockade are augmented. Furthermore, muscle SNA and total norepinephrine spillover are increased in human renovascular hypertension. Renal denervation can delay or blunt 2K1C and Ang II–induced hypertension, suggesting a contribution of increased RSNA or increased renal responsiveness to RSNA. However, RSNA is not necessarily increased in secondary hypertension, and responsiveness of total renal blood flow (RBF) to electrical stimulation of the renal nerves (RNS) in vivo is not augmented.

Neuroeffector gain is the responsiveness of renal neuroeffectors (eg, cortical and medullary perfusion, glomerular filtration rate [GFR], sodium excretion, and renin release) to given levels of RNS or RNF. We hypothesized that the gains of specific neuroeffectors mechanisms are increased in secondary hypertension. Therefore, rabbits with stable hypertension were anesthetized and instrumented for measurement of neuroeffectors responses. Graded RNS was applied and renal norepinephrine spillover was measured to enable dissection of changes in postjunctional responsiveness of neuroeffectors from changes in postganglionic nerve function.

Changes in sympathetic neuroeffector function in secondary hypertension may differ depending on the experimental setting of the kidney. Renal catecholamine content and response of RBF to RNS are diminished in renovascular hypertension. In contrast, renal innervation density and neurally evoked vasoconstriction of arcuate arteries are augmented in Ang II–induced hypertension in rats. Therefore, we studied both the clipped and nonclipped kidneys in 2K1C...
hypothesis and the kidneys of rabbits with Ang II–induced hypertension. This allowed the chronic influences of Ang II to be dissected from the effects of unilateral renal artery stenosis on the clipped and nonclipped kidney.

**Methods**

**Animals and Experimental Design**

Male New Zealand White rabbits (n=31; 2.82±0.03 kg) were studied, according to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. Raising mean ear arterial pressure (MAP) was measured for 1 hour, and arterial blood (1 mL) was collected for plasma renin activity (PRA) determination. Rabbits were then randomized to 4 groups. Under halothane anesthesia, a clip was placed around the left kidney (n=7) or right (n=7) renal artery, an osmotic minipump (Alzet 2ML4, Durect; replaced 22 days later under local analgesia) was inserted subcutaneously for delivery of Ang II (20 to 50 ng kg⁻¹ min⁻¹, Auspep; n=9), or sham surgery was performed (n=8). MAP and PRA were measured 1 and 4 weeks later.

**Terminal Experiment**

**Surgery**

Four to 6 weeks after initial surgery, rabbits were anesthetized with pentobarbital (90 to 150 mg plus 30 to 50 mg h⁻¹ IV; Sigma) and artificially ventilated. Extracellular fluid volume was maintained by intravenous infusion (0.18 mL kg⁻¹ min⁻¹) of a 4:1 mixture of compound sodium lactate and polygeline/electrolyte solution. Rabbits were then randomized to 4 groups. Under halothane anesthesia, a clip was placed around the left kidney (n=7) or right (n=7) renal artery, an osmotic minipump (Alzet 2ML4, Durect; replaced 22 days later under local analgesia) was inserted subcutaneously for delivery of Ang II (20 to 50 ng kg⁻¹ min⁻¹, Auspep; n=9), or sham surgery was performed (n=8). MAP and PRA were measured 1 and 4 weeks later.

**Results**

**Development of Hypertension in Conscious Rabbits**

Before surgery, conscious MAP (79±1 mm Hg), heart rate (181±4 bpm), hematocrit (38.9±0.5%), and PRA (4.5±0.5 ng mL⁻¹) were similar in all of the groups. These variables did not change significantly after sham surgery (P=0.05). By 4 weeks after commencing Ang II infusion or clipping the left or right renal artery, MAP had increased by 24±6%, 17±1%, and 22±6%, respectively (Figure 1), but heart rate had not changed significantly. Hematocrit increased similarly in all groups of hypertensive animals, to average 41.2±0.8% 4 weeks after surgery. PRA had decreased by 1.5±0.7 ng mL⁻¹ after 4 weeks of Ang II infusion but did not change significantly after renal artery clipping (Figure 1).

**Baseline Variables in Anesthetized Rabbits**

Before RNS, these were similar across the 4 groups with only a few exceptions (Table). RBF, GFR, urine flow, and sodium excretion were, respectively, 35%, 44%, 74%, and 64% less in the clipped kidney of 2K1C rabbits than in sham-operated rabbits. Urine flow was 85% greater in the nonclipped kidney of 2K1C rabbits than in sham-operated rabbits. Basal PRA overflow was similar in the clipped kidney and the kidney in sham-operated rabbits but was considerably less in the nonclipped kidney of 2K1C rabbits and in the kidney of Ang II–treated rabbits. After recovery from RNS, all of the variables returned to control levels except for CLDF and hematocrit, which were slightly (13±3% and 2.5±0.6%, respectively) less than control in all 4 of the experimental groups.

**Effects of RNS**

RNS produced frequency-dependent reductions in RBF, CLDF, and MLDF (P<0.001; Figure 2) but little change in MAP (P=0.9). Responses to brief high-frequency RNS (4 to 8 Hz) did not differ significantly according to group, but responses to prolonged stimulation at lower frequencies (0.5 to 2 Hz) did. RBF was reduced less in the nonclipped kidney of 2K1C rabbits, and CLDF was reduced less in the clipped kidney than in the kidney of sham-operated rabbits. RNS at 2 Hz reduced RBF and CLDF by −58% and −59%, respectively, in sham-operated rabbits but by −43% and −52%, respectively, in the nonclipped 2K1C kidney and by −51% and −36% in the clipped 2K1C kidney. RBF and CLDF responses to RNS in Ang II–treated rabbits resembled those in sham-operated rabbits. The reductions in MLDF were greater in Ang II–treated rabbits and the nonclipped kidney of 2K1C rabbits than in sham-operated controls (P<0.05). For example, 2-Hz stimulation reduced MLDF in Ang II–treated rabbits (by −25%) and in the nonclipped kidney in 2K1C rabbits (by −15%) but not in sham-operated rabbits (Figure 2).

RNS reduced GFR, urine flow, and sodium excretion similarly in Ang II–treated rabbits and sham-operated rabbits (Figure 3). However, reductions in sodium excretion in both the clipped and nonclipped kidney in 2K1C rabbits were less
than in sham-operated rabbits. Urine flow followed a similar pattern, although differences between the nonclipped kidney in 2K1C rabbits and sham-operated rabbits were not statistically significant ($P=0.08$). Reductions in GFR tended to be less in the nonclipped kidney in 2K1C rabbits than in sham-operated rabbits ($P=0.06$).

RNS increased renal PRA overflow and renal norepinephrine spillover (Figure 4). Increases in renal norepinephrine spillover tended to be blunted in the clipped kidney of 2K1C rabbits ($P=0.08$) but were otherwise similar in all 4 of the groups. Increases in renal PRA overflow were greater in the sham-operated rabbit kidney ($+439 \pm 79$ ng min$^{-1}$ at 2 Hz) than in the clipped ($+134 \pm 78$ ng min$^{-1}$ at 2 Hz) and nonclipped ($+156 \pm 85$ ng min$^{-1}$ at 2 Hz) kidney of 2K1C rabbits or the Ang II–treated rabbit kidney ($+211 \pm 112$ ng min$^{-1}$ at 2 Hz).

**Baseline Levels of Hemodynamic and Renal Variables in Anesthetized Rabbits**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham</th>
<th>Ang II</th>
<th>2K1C Clip</th>
<th>2K1C Nonclip</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>72±1</td>
<td>76±4</td>
<td>82±2</td>
<td>77±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>231±10</td>
<td>245±13</td>
<td>240±10</td>
<td>249±9</td>
</tr>
<tr>
<td>RBF, mL min$^{-1}$</td>
<td>23.9±1.9</td>
<td>21.2±2.0</td>
<td>15.5±2.4*</td>
<td>25.5±2.8</td>
</tr>
<tr>
<td>CLDF, units</td>
<td>238±21</td>
<td>224±21</td>
<td>187±30</td>
<td>247±19</td>
</tr>
<tr>
<td>MLDL, units</td>
<td>46±5</td>
<td>38±6</td>
<td>46±8</td>
<td>50±10</td>
</tr>
<tr>
<td>Hct, %</td>
<td>34.0±1.0</td>
<td>36.9±1.3</td>
<td>36.0±0.9</td>
<td>38.0±2.2</td>
</tr>
<tr>
<td>GFR, mL min$^{-1}$</td>
<td>4.08±0.34</td>
<td>3.52±0.98</td>
<td>2.28±0.99*</td>
<td>3.95±0.81</td>
</tr>
<tr>
<td>Urine flow, $\mu$L min$^{-1}$</td>
<td>325±63</td>
<td>374±76</td>
<td>86±55*</td>
<td>599±159*</td>
</tr>
<tr>
<td>FEvol, %</td>
<td>8.2±1.8</td>
<td>19.0±8.9</td>
<td>4.1±1.7</td>
<td>15.8±2.9</td>
</tr>
<tr>
<td>FEvol, %</td>
<td>6.6±1.7</td>
<td>17.1±9.5</td>
<td>4.4±1.7</td>
<td>11.4±2.2</td>
</tr>
<tr>
<td>Na$^+$ excretion, $\mu$mol min$^{-1}$</td>
<td>33.0±6.9</td>
<td>36.6±6.7</td>
<td>11.8±7.4*</td>
<td>51.9±14.3</td>
</tr>
<tr>
<td>Arterial PRA, ng mL$^{-1}$</td>
<td>16.9±4.6</td>
<td>11.5±5.6</td>
<td>20.9±5.8</td>
<td>25.0±9.7</td>
</tr>
<tr>
<td>Renal vein PRA, ng mL$^{-1}$</td>
<td>24.6±8.0</td>
<td>12.8±5.8</td>
<td>34.9±12.7</td>
<td>23.0±8.5</td>
</tr>
<tr>
<td>Renal PRA overflow, ng min$^{-1}$</td>
<td>106.5±48.7</td>
<td>18.4±5.9</td>
<td>114.4±60.8</td>
<td>−28.1±14.6†</td>
</tr>
<tr>
<td>Renal NE extraction, %</td>
<td>56.4±3.3</td>
<td>55.7±3.4</td>
<td>52.6±3.5</td>
<td>41.9±4.2*</td>
</tr>
<tr>
<td>Renal NE spillover, ng min$^{-1}$</td>
<td>1.4±0.5</td>
<td>0.5±0.5</td>
<td>1.5±1.3</td>
<td>1.2±0.8</td>
</tr>
<tr>
<td>No. per group</td>
<td>7 to 8</td>
<td>8 to 9</td>
<td>6 to 7</td>
<td>6 to 7</td>
</tr>
</tbody>
</table>

Values are mean±SEM using between animal variance. HR indicates heart rate; RBF, renal blood flow; Hct, hematocrit; FEvol, fractional urine excretion; FEvol, fractional excretion of sodium; NE, norepinephrine.

*P<0.05, †P<0.001 for comparison of hypertensive groups with sham-operated controls.
There were strong predictive relationships between (Log10) renal norepinephrine spillover and RBF, CLDF, GFR, urine flow, and sodium excretion ($P < 0.001$ in all cases). The slopes of these relationships were indistinguishable in the 4 groups of rabbits ($P > 0.12$). Renal PRA overflow correlated strongly with (Log10) renal norepinephrine spillover ($P < 0.001$), but the slope of this relationship was less in hypertensive rabbits than in sham-operated rabbits ($P < 0.001$; Figure 5). Across all 4 of the groups, there was no statistically significant relationship between MLDF and (Log10) renal norepinephrine spillover ($P = 0.38$). However, a highly significant relationship was present in hypertensive rabbits ($P = 0.003$) but not sham-operated rabbits ($P = 0.10$). Thus, the slope of this relationship differed in hypertensive rabbits compared with sham-operated rabbits ($P = 0.001$; Figure 5).

**Postmortem Measurements**

The left ventricle of sham-operated rabbits ($1.31 \pm 0.03$ g kg$^{-1}$) weighed less than that of Ang II–treated rabbits ($1.56 \pm 0.04$ g kg$^{-1}$) and of rabbits with a clip on the right or left renal artery (average $1.47 \pm 0.03$ g kg$^{-1}$; $P < 0.01$ for comparison of hypertensive and sham-operated rabbits). Kidney weight was similar in sham-operated ($3.37 \pm 0.11$ g kg$^{-1}$) and Ang II–treated ($3.61 \pm 0.10$ g kg$^{-1}$; $P = 0.21$) rabbits. However, in 2K1C hypertensive rabbits, the clipped kidney had atrophied (2.71 ± 0.21 g kg$^{-1}$) and the nonclipped kidney had undergone hypertrophy ($3.95 \pm 0.15$ g kg$^{-1}$; $P < 0.01$ compared with sham-operated).

**Discussion**

We determined whether the gain of renal neuroeffector mechanisms is altered in Ang II–induced hypertension and in

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Renal hemodynamic responses to electrical RNS. Symbols and error bars represent the mean±SEM of percentage changes from control calculated between animals. $*P < 0.05$ for comparisons of hypertensive groups with sham-operated group. Abbreviations are as for Table 1. The break in the abscissa denotes that responses to ≥2 Hz were averaged over the last 15 minutes of a 20-minute stimulus train, whereas those to 4 and 8 Hz were averaged over the last minute of a 3-minute stimulus train.

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Responses of renal excretory variables to electrical RNS. Symbols and error bars are as for Figure 2. Asterisks are as for Figure 2. Abbreviations are as for Table 1.

![Figure 4](http://hyper.ahajournals.org/)

**Figure 4.** Responses of renal PRA overflow and norepinephrine (NE) spillover to electrical stimulation of renal nerves. Symbols and error bars are as for Figure 2 and represent the mean±SEM of changes from control calculated between animals. $**P < 0.01$ for hypertensive groups vs sham-operated group. Abbreviations are as for Table 1.
2K1C hypertension. Our rationale was that increased gain of one or more renal neuroeffector mechanism could contribute to the development and/or maintenance of hypertension. The major findings were that renal hemodynamic responses to RNS were altered in the kidneys of hypertensive rabbits in a regionally selective manner. Responses of RBF and CLDF (a measure of outer cortical perfusion) to RNS were blunted in the nonclipped and clipped kidneys, respectively, in 2K1C hypertension. In contrast, responses of MLDF (a measure of medullary perfusion) to low-frequency RNS (≤2 Hz) were enhanced in kidneys of hypertensive rabbits. Prolonged RNS at 2 Hz did not reduce MLDF in sham-operated rabbits, consistent with our previous findings, but reduced MLDF in all groups of hypertensive rabbits. However, RNS-induced reductions in GFR, urine flow, and sodium excretion were not enhanced in kidneys from hypertensive animals. Indeed, these responses also appeared to be blunted, at least in the nonclipped kidney in 2K1C hypertension. We also found that RNS-induced renin overflow was greatly attenuated in all of the hypertensive groups studied.

Thus, all of the renal neuroeffectors we studied, only neural control of medullary perfusion appears to have increased gain and is, therefore, the only one that could be considered prohypertensive. Reductions in medullary perfusion induced by RNS are likely mediated chiefly by constriction of juxtamedullary arterioles and/or outer medullary descending vasa recta, which are densely innervated. The medullary circulation is pivotal in long-term blood pressure control, chiefly through its influence on tubular sodium reabsorption, such that increased sensitivity of medullary vascular elements to RSNA could contribute to development of hypertension. Similar responses of MLDF to RNS were observed in the kidneys of rabbits with Ang II–induced hypertension and in both the clipped and nonclipped kidney in 2K1C hypertension, indicating that factors common to all 3 of the conditions are responsible for enhancing responsiveness of the medullary circulation to RNS. These putative factors are unlikely to include hypertension, per se, because MAP under anesthesia was similar in all 4 groups of rabbits, and acute changes in renal perfusion pressure have little effect on the responses of MLDF to RNS. There is good evidence, however, that the activity of the intrarenal renin–angiotensin system is increased in Ang II–induced hypertension and also in both the clipped and unclipped kidney in 2K1C hypertension. This is likely to have at least 2 actions that could enhance neurally evoked vasoconstriction in the medullary circulation. First, endogenous Ang II appears to enhance neurally evoked vasoconstriction in the medullary circulation through activation of both Ang II type 1 receptors and Ang II type 2 receptors. Second, Ang II increases superoxide production and, thus, reduces NO bioavailability. Endogenous NO acts to blunt responses of MLDF to low- (≤2 Hz) but not high- (≥4 Hz) frequency RNS, so reduced NO bioavailability would be expected to enhance responses of medullary perfusion to RNS at low but not high frequencies, just as we observed in the hypertensive animals in the current study. Consistent with this notion, oxidative stress blunts NO-dependent attenuation of sympathetic vasoconstriction in the hindlimb of rats with angiotensin-independent and 2K1C hypertension.

Responses of the cortical circulation and of GFR, urine flow, and sodium excretion to RNS were not enhanced in hypertension. Indeed, in the case of 2K1C hypertension, the gains of these renal neuroeffector mechanisms were, if anything, reduced compared with normotensive rabbits. These observations are consistent with those of Fink and Brody, who demonstrated impaired neurogenic control of the renal vasculature in 2-kidney 1-wrap hypertension in rats. RNS-induced reductions in RBF, CLDF, GFR, urine flow, and sodium excretion in rabbits with Ang II–induced hypertension were indistinguishable from those in normotensive rabbits, as was found previously for RBF alone. Collectively, these data indicate that changes in the sensitivity of cortical perfusion and sodium excretion to RNS in secondary hypertension depend on the precise experimental setting of the kidney. Exposure of the kidney to elevated circulating levels of Ang II, per se, appears to have little impact, but clipping one renal artery appears to set in train changes in the gains of these renal sympathetic neuroeffectors in both the clipped and unclipped kidney.

The fact that RNS-induced reductions in sodium excretion were not enhanced in hypertensive animals may seem at odds with the enhanced response of MLDF to RNS in hypertension, because reduced medullary perfusion should have an antinatriuretic effect. However, the effects of changes in medullary perfusion on salt and water reabsorption likely depend on slowly evolving changes in renal interstitial...
hydrostatic pressure. The relatively short clearance periods (15 minutes) in the current study may, therefore, not have allowed full expression of the effects of altered medullary perfusion on renal excretory function. Nevertheless, prolonged reductions in medullary perfusion induced by ongoing RSNA would be expected to enhance tubular sodium reabsorption and, thus, increase extracellular fluid volume and the long-term set point of arterial pressure.

RNS increased PRA overflow less in all of the hypertensive rabbit groups than in sham-operated controls. Interactions between hemodynamic factors and neural control of renin release have been studied, but effects of Ang II-negative feedback on neurally mediated renin release have received little attention. Our present observations are, therefore, novel and indicate that Ang II negative feedback largely overrides neural stimulation of renin release.

Arterial PRA was greatly reduced in Ang II–induced hypertension, consistent with the negative feedback influence of Ang II on renal renin release and our finding of reduced basal PRA overflow from the denervated kidney in Ang II-treated rabbits under anesthesia. Our finding that arterial PRA was not increased in 2K1C hypertension may seem surprising, because this model is considered “renin dependent.” However, hypertension without elevated PRA is frequently observed in established 2K1C hypertension in rabbits and other species. Nevertheless, increased activity of the intrarenal renin–angiotensin system is often observed in both the clipped and nonclipped kidney in 2K1C hypertension, which could act to inhibit renal renin release.

A major contribution of the current study has been to distinguish between presynaptic and postsynaptic mechanisms in renal neuroeffector function by using renal norepinephrine spillover. We could not detect significant differences in the effects of RNS on renal norepinephrine spillover between the normotensive and hypertensive groups of rabbits. However, RNS tended to increase renal norepinephrine spillover less in the clipped kidney in 2K1C hypertension than in the kidney of normotensive rabbits, consistent with the notion that renovascular hypertension is associated with a defect in norepinephrine storage in the renal nerves. Nevertheless, our data indicate that norepinephrine release from renal sympathetic nerves, for any given frequency of RNS, is not altered in Ang II–induced hypertension or in the nonclipped kidney in 2K1C hypertension. Our data also suggest that the major changes in sympathetic neuroeffector function that we observed are mediated chiefly at the postjunctional level. Consistent with this, we found that the relationships of renal norepinephrine spillover to renal PRA overflow and MLDF were significantly different in hypertensive compared with normotensive rabbits. Thus, the increased sensitivity of medullary perfusion and reduced sensitivity of renal renin release to RNS, observed in hypertensive rabbits, appears to be because of changes in the sensitivity of these neuroeffectors to sympathetic neurotransmitters, such as norepinephrine.

In the current study, we examined the renal neuroeffector mechanisms under anesthesia, which may be considered a disadvantage. However, as has been observed previously in Ang II–induced hypertension, differences in MAP between the 3 groups of hypertensive rabbits and sham-operated controls were largely abolished by pentobarbital anesthesia. This may reflect the sympatholytic effects of pentobarbital. Regardless, it aids interpretation of our experiment by removing potentially confounding effects of systematic differences in MAP between the rabbits. We confirmed in the present study that the 2K1C procedure and the Ang II infusion did indeed produce moderate hypertension, which was similar in the 3 groups.

Perspectives
Our present results provide a new perspective of how changes in renal sympathetic neuroeffector function could contribute to the pathogenesis of Ang II–induced and 2K1C hypertension. We can reject the hypothesis that the sensitivity of renin release to renal nerve activation is enhanced in these forms of hypertension, because RNS-induced increases in PRA overflow were blunted in the kidneys of all of the hypertensive rabbits that we studied. Our results also do not support the hypothesis that the sensitivity of the renal cortical circulation to renal nerve activation is increased in these models of hypertension. However, our results are consistent with the hypothesis that the sensitivity of medullary perfusion to renal nerve activation is increased in both 2K1C hypertension and Ang II–induced hypertension. The precise mechanisms underlying this phenomenon remain unknown, but available evidence suggests that reduced NO bioavailability secondary to Ang II–induced oxidative stress and direct effects of endogenous Ang II on responses of the medullary circulation to neural activation are prime candidates that should be further investigated. Future studies should also investigate the contribution of neural control of medullary perfusion to the development of these forms of secondary hypertension.

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Disclosures
None.

References


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