Systemic and Regional Hemodynamic Responses to Tempol in Angiotensin II–Infused Hypertensive Rats

Akira Nishiyama, Toshiki Fukui, Yoshihide Fujisawa, Matlubur Rahman, Run-Xia Tian, Shoji Kimura, Youichi Abe

Abstract—Recent studies have indicated that angiotensin II (Ang II) can stimulate oxidative stress. The present study was conducted to assess the contribution of oxygen radicals to hypertension and regional circulation during Ang II–induced hypertension. With radioactive microspheres, the responses of systemic and regional hemodynamics to the membrane-permeable, metal-independent superoxide dismutase mimetic 4-hydroxy-2,2,6,6-tetramethyl piperidinoxyl (tempol) were assessed in conscious Ang II–infused hypertensive rats. Ang II–infused rats (80 ng/min SC for 12 days; n=25) showed higher mean arterial pressure (MAP: 161±4 mm Hg) and total peripheral resistance (TPR: 1.59±0.08 mm Hg·min⁻¹·mL⁻¹) than vehicle-infused normotensive rats (116±3 mm Hg and 0.95±0.04 mm Hg·min⁻¹·mL⁻¹, respectively; n=23). The blood flow rates in the brain, spleen, large intestine, and skin were significantly reduced in Ang II–infused rats compared with vehicle-infused rats, whereas rates in the lung, heart, liver, kidney, stomach, small intestine, mesenterium, skeletal muscle, and testis were similar. Vascular resistance was significantly increased in every organ studied except the lung, in which the resistance was similar. Tempol (216 μmol/kg IV) significantly reduced MAP by 30±4% from 158±7 to 114±5 mm Hg and TPR by 35±6% from 1.57±0.17 to 0.95±0.04 mm Hg·min⁻¹·g⁻¹ in Ang II–infused rats (n=9) but had no effect on these parameters in vehicle-infused rats (n=8). In Ang II–infused rats, tempol did not affect regional blood flow but significantly decreased vascular resistance in the brain (29±6%), heart (31±6%), liver (37±7%), kidney (30±7%), small intestine (38±6%), and large intestine (47±7%). Ang II–infused hypertensive rats showed doubled vascular superoxide production (assessed with lucigenin chemiluminescence), which was normalized by treatment with tempol (3 mmol/L, n=7). Further studies showed that the NO synthase inhibitor, N’-nitro-L-arginine methyl ester (11 μmol·kg⁻¹·min⁻¹·IV, n=11) markedly attenuated the systemic and regional hemodynamic responses of tempol in Ang II–infused rats. These results suggest that in this model of hypertension, oxidative stress may have contributed to the alterations in systemic blood pressure and regional vascular resistance through inactivation of NO. (Hypertension. 2001;37:77-83.)

Key Words: angiotensin II ■ oxygen radicals ■ hypertension, renovascular ■ nitric oxide ■ hemodynamics ■ microspheres ■ tempol

Angiotensin II (Ang II) exerts a powerful hypertensogenic influence when its level of activity is not appropriate for existing physiological status.1,2 The chronic infusion of Ang II into uninephrectomized rats mimics the pattern of hypertension observed in 2-kidney, 3-clip (2K1C) Goldblatt renovascular hypertension.1,2 The mechanisms responsible for the progressive nature of Ang II–induced hypertension are multifarious and incompletely understood. A growing body of evidence indicates that Ang II can stimulate oxidative stress,3–11 which may participate in the vasoconstrictor effect of Ang II.10,12,13 In vitro studies have shown that incubation of cultured vascular smooth muscle cells,3 aortic adventitial fibroblasts,4 and mesangial cells5 with Ang II increases superoxide production. Rajagopalan et al6 and Fukui et al7 reported that treatment of rats with Ang II (0.7 mg·kg⁻¹·d⁻¹·SC for 5 days) elicits hypertension associated with a significant increase in superoxide production from aortic segments. It was also demonstrated that renovascular hypertension in 2K1C Goldblatt rats8 is associated with increased vascular superoxide. Laursen et al9 showed that treatment with liposome-encapsulated superoxide dismutase (SOD) significantly reduces blood pressure in Ang II–infused hypertensive rats while having no effects on blood pressure in rats with norepinephrine-induced hypertension. Recent studies performed in conscious swine have demonstrated that chronic Ang II infusion (10 ng·kg⁻¹·min⁻¹·IV for 28 days) elicits...
hypertension and significantly increases plasma-free isoprostane, isoprostane F3,ω,11 which was recently proposed as a marker of oxidative stress.10,14,15

Although these observations implicate a role for oxidative stress in Ang II–induced hypertension, the extent to which oxygen radicals contribute to regional hemodynamic control in different vascular beds remains undetermined. Therefore, the objective of the present study was to determine whether oxidative stress differentially participates in the regulation of regional vascular resistance during the development of Ang II–induced hypertension. Using a radioactive microsphere method,16,17 we characterized the systemic and regional hemodynamics in conscious Ang II–infused hypertensive rats and evaluated the effects of acute systemic administration of the membrane-permeable, metal-independent SOD mimetic 4-hydroxy-2,2,6,6-tetramethyl piperidinoxyl (tempol), which has been shown to be a stable spin trap18 and to scavenge superoxide anions in vitro.19 In addition, to determine whether Ang II–induced superoxide anion production may influence systemic and regional hemodynamics through the inactivation of NO, the effects of tempol were examined in Ang II–infused rats pretreated with the NO synthase inhibitor L-NMMA. We also examined the effect of tempol on vascular superoxide production in Ang II–infused hypertensive rats.

Methods

Animal Preparation

Male Sprague-Dawley rats were housed in separate cages and maintained in a temperature-room regulated on a 12-hour light/dark cycle. Throughout the experiments, animals had free access to water and to standard rat chow. All surgical and experimental procedures were performed according to the guidelines for the care and use of animals as established by the Kagawa Medical University.

Rats weighing 270 to 310 g at the beginning of the experiments were anesthetized with sodium pentobarbital (50 mg/kg IP), and an osmotic minipump (model 2002; Alza Co) was implanted subcutaneously at the dorsum of the neck. Rats were selected at random to receive Ang II (Sigma Chemical Co) infusion (n = 25) at a rate of 80 ng/min or vehicle (n = 23; 5% acetic acid) for a period of 12 days. Eleven days after beginning treatment, rats were anesthetized with sodium pentobarbital (50 mg/kg IP), and catheters were implanted as described previously.16,17 Animals were allowed to recover for 24 hours before initiation of the experimental procedures.

Measurements of Systemic and Regional Hemodynamics

The femoral arterial catheter was connected to the pressure transducer, and mean arterial pressure (MAP) was continuously recorded on a multichannel polygraph (Nihondenki-Sanei). Radioactive microspheres were used to measure the cardiac output (CO) and regional blood flow, as previously reported.16,17 Briefly, 2 different radionuclide-labeled microspheres (51Cr and 89Sr; New England Nuclear), 15 ± 3 μm in diameter, were used. In vehicle-infused rats (n = 23) and Ang II–infused rats (n = 25), 0.25 mL saline solution containing 75 000 microspheres (51Cr) was injected from a catheter placed in the left ventricle via the right carotid artery. The injection procedure was performed during a 15-second period. Arterial blood samples for reference blood were obtained from the femoral arterial catheter with a withdrawal pump at a rate of 0.55 mL/min starting immediately before the injection of the microspheres and ending 60 seconds later.

In these rats, systemic and regional responses to tempol (Sigma Chemical Co) at 72 and 216 μmol/kg IV were determined in vehicle-infused rats (n = 7 and 8, respectively) and Ang II–infused rats (n = 8 and 9, respectively). Fifteen minutes after the first injection of microspheres (51Cr), tempol was administered at a volume of 0.5 mL/kg from a catheter placed in the femoral vein, and then saline solution containing the second microspheres (89Sr) was injected.

In a separate experimental series, systemic and regional responses to a higher dose of tempol (216 μmol/kg IV) were determined in Ang II–infused rats pretreated with L-NMMA (11 μmol · kg −1 · min −1 IV, n = 11; Sigma Chemical Co). Twenty minutes after the L-NMMA infusion was started, the first injection of microspheres (51Cr) was made. Subsequently, tempol was administered, and then the second injection of microspheres (89Sr) was made as described earlier.

### Table 1. Systemic Hemodynamics in Vehicle-Infused Normotensive Rats and Ang II–Infused Hypertensive Rats

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Vehicle-Infused Rats</th>
<th>Ang II–Infused Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>116 ± 3</td>
<td>161 ± 4†</td>
</tr>
<tr>
<td>CO, mL/min</td>
<td>128 ± 5</td>
<td>104 ± 4*</td>
</tr>
<tr>
<td>TPR, mm Hg · min⁻¹ · mL⁻¹</td>
<td>0.95 ± 0.04</td>
<td>1.59 ± 0.08†</td>
</tr>
</tbody>
</table>

All values are mean ± SEM. *P < 0.05, †P < 0.01 vs vehicle-infused rats.
After termination of the injection of microspheres, the animals were killed with an excess dose of sodium pentobarbital. The brain, lungs, heart, liver, spleen, kidneys, stomach, intestines (small and large), mesenterium, skin, hindlimb skeletal muscle, and testis were removed and weighed. The activities of each batch of microspheres in stock solution, reference blood, and tissue samples were analyzed with a \( \gamma \)-scintillation counter. The CO, total peripheral resistance (TPR), absolute organ blood flow, organ vascular resistance, and fraction of CO to each organ and tissue were calculated as previously described.\(^{16,17}\)

**Measurement of Vascular Superoxide Anion Production**

In a separate experimental series, superoxide anion production in aortic segments from vehicle-infused rats (\( n = 5 \)) and Ang II–infused rats (\( n = 7 \)) were determined with the use of lucigenin chemiluminescence. The details of this assay have been described previously.\(^{20}\) Briefly, the animals were killed with an excess dose of sodium pentobarbital, and the aorta was quickly removed. Perivascular tissue was carefully removed, and the vessels were repeatedly washed to remove adherent blood cells and cut into 5-mm ring segments. The rings were placed in chilled bicarbonate buffer that was composed of (in mmol/L) NaCl 118.3, KCl 4.7, CaCl\(_2\) 2.5, KH\(_2\)PO\(_4\) 1.2, MgSO\(_4\) 1.2, NaHCO\(_3\) 25.0, glucose 5.5, and EDTA 0.026 and was bubbled continuously with 95% O\(_2\) -5% CO\(_2\) to maintain pH 7.4 and were allowed to equilibrate for 30 minutes at 37°C. After equilibration, rings were rinsed with prewarmed (37°C) modified Krebs-HEPES buffer composed of (in mmol/L) NaCl 119, HEPES 20, KCl 4.6, MgSO\(_4\) 1.0, NaHPO\(_4\) 0.15, KH\(_2\)PO\(_4\) 0.4, NaHCO\(_3\) 25, CaCl\(_2\) 1.2, and glucose 5.5 (pH 7.4). Rings were placed in 1 mL Krebs-HEPES buffer containing lucigenin (250 \( \mu \)mol/L) and equilibrated in the dark for 10 minutes at 37°C. The chemiluminescence was then recorded every 30 seconds for 15 minutes with a luminescence reader (BLR-301; Aloka). Lucigenin chemiluminescence was expressed as counts per minute per milligram of dry tissue weight. After measurements of basal production of superoxide anion, tempol (3 mmol/L) was administered in each sample. This concentration was estimated from the blood concentration of tempol at 216 \( \mu \)mol/kg IV.

**Statistical Analysis**

All values are expressed as mean±SEM. For each variable, simultaneous multiple comparisons of group mean values were made with the use of ANOVA and Fisher’s PLSD test. Statistical comparisons of the differences in the responses were performed with ANOVA followed by the Newman-Keuls test. \( P<0.05 \) was taken to indicate significant differences between data mean values.

**Results**

**Systemic and Regional Hemodynamics in Ang II–Infused Rats**

The systemic parameters for the 2 groups of rats used in the microsphere experiments are presented in Table 1. Compared with those in vehicle-infused normotensive rats (\( n = 23 \)), Ang II infusion for 12 days resulted in a significant increase in MAP (\( P<0.01 \)) and TPR (\( P<0.01 \)) and decrease in CO (\( P<0.05; n = 25 \), respectively). Figures 1 and 2 illustrate the individual changes in regional blood flow and calculated vascular resistance, respectively. The blood flow rates in the

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Vehicle-Infused Rats</th>
<th>Ang II-Infused Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1.53±0.07</td>
<td>1.17±0.11*</td>
</tr>
<tr>
<td>Lung</td>
<td>0.72±0.08</td>
<td>0.84±0.19</td>
</tr>
<tr>
<td>Heart</td>
<td>5.24±0.38</td>
<td>6.01±0.38</td>
</tr>
<tr>
<td>Liver</td>
<td>14.2±1.1</td>
<td>14.7±1.2</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.39±0.07</td>
<td>0.65±0.08*</td>
</tr>
<tr>
<td>Kidney</td>
<td>14.1±0.7</td>
<td>13.1±0.8</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.67±0.14</td>
<td>1.88±0.14</td>
</tr>
<tr>
<td>Small intestine</td>
<td>5.43±0.49</td>
<td>5.96±0.51</td>
</tr>
<tr>
<td>Large intestine</td>
<td>2.62±0.19</td>
<td>2.99±0.16</td>
</tr>
<tr>
<td>Mesenterium</td>
<td>2.14±0.26</td>
<td>2.16±0.19</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>0.55±0.07</td>
<td>0.66±0.09</td>
</tr>
<tr>
<td>Skin</td>
<td>0.58±0.05</td>
<td>0.32±0.04*</td>
</tr>
<tr>
<td>Testis</td>
<td>0.64±0.04</td>
<td>0.67±0.04</td>
</tr>
</tbody>
</table>

All values are mean±SEM.

*\( P<0.05 \) vs vehicle-infused rats.
brain, spleen, large intestine, and skin were significantly reduced in Ang II–infused rats compared with vehicle-infused animals \( (P < 0.05, \text{respectively}) \), but there were no statistically significant differences in the blood flow rates in the lung, heart, liver, kidney, stomach, small intestine, mesenterium, skeletal muscle, or testis between these animals (Figure 1). Ang II–infused rats showed widespread increases in vascular resistance in the brain, heart, liver, kidney, stomach, intestine (small and large), mesenterium, skeletal muscle, skin, and testis \( (P < 0.05, \text{respectively}) \) compared with vehicle-infused rats, but there were no statistically significant changes in vascular resistance in other organs or tissues (Figure 2). The average percent distribution of CO to each organ or tissue is presented in Table 2. The percent distribution of CO to the brain, spleen, and skin in Ang II–infused rats was significantly lower than that in vehicle-infused rats \( (P < 0.05, \text{respectively}) \). In contrast, there were no significant differences in the percent distribution of CO to the lung, heart, liver, kidney, stomach, intestine (small and large), mesenterium, skeletal muscle, or testis between these animals (Table 2).

**Systemic and Regional Hemodynamic Effects of Tempol**

Figure 3 shows the MAP and TPR responses to tempol in vehicle-infused and Ang II–infused rats. Tempol at 72 \( \mu \text{mol/kg} \) did not cause any significant changes in these parameters in vehicle-infused rats \( (n = 7 \text{ and 8}) \), respectively. In contrast, tempol resulted in dose-dependent reductions in MAP and TPR in Ang II–infused rats. A higher dose of tempol (216 \( \mu \text{mol/kg} \)) significantly reduced MAP by 30±4% from 158±7 to 114±5 mm Hg \( (P < 0.01) \) and TPR by 35±6% from 1.57±0.17 to 0.95±0.04 mm Hg \( \cdot \text{min}^{-1} \cdot \text{g}^{-1} \) \( (P < 0.01, n = 9, \text{Figures 3C and 3D}) \). Tempol had no effect on CO, the blood flow to any of the organ beds, or the percent distribution of CO to each organ in vehicle- and Ang II–infused rats (data not shown). In Ang II–infused rats, tempol resulted in dose-dependent reductions in vascular resistance in the brain, heart, liver, kidney, and large intestine \( (P < 0.05, \text{respectively}) \) without significant changes in vascular resistance in other organs or tissues (Figure 4). In contrast, tempol did not affect regional vascular resistance in vehicle-infused normotensive animals (Figure 4).

**Systemic and Regional Hemodynamic Effects of Tempol During NO Synthesis Inhibition**

A 20-minute infusion of L-NAME \( (11 \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \) significantly increased MAP from 155±6 to 174±7 mm Hg in Ang II–infused rats \( (P < 0.01, n = 11) \). Tempol (216 \( \mu \text{mol/kg} \)) slightly but significantly decreased MAP by 7±1% to 164±7 mm Hg \( (P < 0.05) \). On the basis of group comparisons,
however, the MAP responses to tempol in L-NAME–treated Ang II–infused rats were significantly smaller than those observed in Ang II–infused rats, as shown in Figure 5 (P<0.01). L-NAME significantly increased TPR in Ang II–infused rats, which was not altered by tempol administration (from 3.59±0.31 to 3.47±0.37 mm Hg·min⁻¹·g⁻¹, Figure 5). In Ang II–infused rats, CO was significantly reduced by L-NAME treatment and remained unchanged after tempol administration (data not shown). Ang II–infused rats treated with L-NAME showed markedly reduced blood flow rates and increased vascular resistance in all organs or tissues studied, which were not altered by tempol administration (data not shown).

**Effect of Tempol on Vascular Superoxide Anion Production**

Lucigenin chemiluminescence from aortic segments of vehicle-infused normotensive rats averaged 9.4±1.0 counts·10⁻³·mg dry tissue wt vessel⁻¹·min⁻¹ (n=5). In Ang II–infused hypertensive rats (n=7), lucigenin chemiluminescence was 2.7-fold higher than that of vehicle-infused animals (P<0.01, Figure 6). Treatment with tempol (3 mmol/L) significantly decreased lucigenin chemiluminescence from aortic segments of vehicle- and Ang II–infused animals as shown in Figure 6 (P<0.01).

**Discussion**

In agreement with previous studies,1,2,21 the chronic infusion of Ang II produced a significant elevation in MAP associated with a significant increase in TPR and decrease in CO. Tempol, which is a membrane-permeable SOD mimic18 and suggested to be a scavenger of superoxide anions,14,18,19,22 significantly decreased MAP and TPR with no change in CO in conscious Ang II–induced hypertensive rats while having no effect on these parameters in vehicle-infused normotensive rats. These results support the hypothesis of recent studies1,4,6–13 that suggests oxidative stress, at least in part, participates in the production of Ang II–induced hypertension. To obtain further insight with regard to the role of oxidative stress in the regulation of regional circulation in Ang II–induced hypertension, we characterized the regional hemodynamics in conscious Ang II–infused hypertensive rats and examined the changes occurring in response to tempol.

Although several studies have indicated that Ang II differentially influences the resting vascular tone of various vascular beds,23,24 to our knowledge, no previous investigations have reported the assessment of regional hemodynamics in Ang II–infused hypertensive rats. We found that the blood flow rates in the brain, spleen, large intestine, and skin of Ang II–infused hypertensive rats were significantly reduced compared with those of vehicle-infused normotensive animals. In contrast, the blood flow rates in the lung, heart, liver, kidney, stomach, small intestine, mesenterium, skeletal muscle, and...
tests were maintained in Ang II–infused rats. These results indicate that regional hemodynamic responses to chronically elevated Ang II levels were not uniform among the organs studied. Possible explanations for these differences may be regional heterogeneity of responsiveness to Ang II,23,24 Ang II production,25 AT1 receptor populations,26 and the sensitivity (or expression) of local endogenous vasodilators23,24,27 during the development of Ang II–induced hypertension. In particular, these possibilities have been well studied in the kidney.25,27–33 During the development of Ang II–induced hypertension, renal microvascular reactivity to Ang II is significantly enhanced.27,28 It was also demonstrated that in this model of hypertension, intrarenal Ang II levels increase to a greater extent than can be explained from the circulating levels,25,29 and the tissue specific elevations of intrarenal Ang II involve both endogenous formation and accumulation of circulating Ang II.29,30 Recent studies have shown that Ang II–induced hypertension in the rat is accompanied by elevations in adrenal AT1, mRNA levels and maintenance of kidney and liver AT1 mRNA and protein levels.31 Furthermore, studies at the whole kidney level32 and the renal microvasculature level13 have demonstrated the involvement of enhanced activity of NO in counteraction of the elevated Ang II–dependent influences on renal hemodynamics in Ang II–infused hypertensive rats. Collectively, these data suggest that the mechanisms responsible for the heterogeneity of regional hemodynamics in Ang II–infused hypertensive rats may be multifariable. Further studies are needed to resolve the tissue specific role of Ang II in the regulation of regional hemodynamics in Ang II–induced hypertension.

To assess whether tempol acts as a scavenger of superoxide anions, the effect of tempol on superoxide anion production in aortic segments was determined by the use of lucigenin chemiluminescence. In agreement with previous reports,6–9 we observed that Ang II–induced hypertension is associated with increased vascular superoxide production. We also found that tempol normalized vascular superoxide production in Ang II–infused hypertensive rats. These results suggest that the acute administration of tempol decreased oxidative stress in Ang II–infused hypertensive rats. The results of the present study show that tempol significantly decreased MAP and TPR without significant change in CO in Ang II–infused hypertensive rats. In view of the antihypertensive as well as vasodilator effects of tempol, the possibility exists that tempol may have affected a regional hemodynamic abnormality observed in the hypertensive stage. In the present study, it was observed that tempol did not change the blood flow to any organ or tissue in Ang II–infused hypertensive rats. These results suggest that in this form of hypertension, oxidative stress may not be the primary mediator of vasoconstriction in each vascular bed. However, tempol significantly decreased vascular resistance in the brain, heart, liver, kidney, small intestine, and large intestine without causing significant changes in the vascular resistance of other organs or tissues. Thus, not all organs and tissues did contribute equally to tempol-induced reduction in TPR in Ang II–infused hypertensive rats. This heterogeneity of tempol-induced regional vascular responsiveness provides support for the hypothesis that oxygen radicals are released in local vascular beds and differentially contribute to the resting vascular tone in Ang II–induced hypertensive rats.

The mechanisms of the reductions in systemic and regional vascular resistance through the scavenging of superoxide anions remain unclear. One possible explanation is that Ang II–induced release of vascular superoxide radicals inactivates NO and thereby diminishes its vasodilatory actions.10,12,13,22 In support of this possibility, Rajagopalan et al8 and Laursen et al9 reported that increases in vascular superoxide production are associated with impaired vasodilator relaxation in response to acetylcholine, nitroglycerin, and nitroprusside in Ang II–infused hypertensive rats. Along similar lines, it was shown that renovascular hypertension in 2K1C Goldblatt rats is associated with increased vascular superoxide, which leads to an impaired vasodilator response to acetylcholine and nitroglycerin.8 Furthermore, Schnackenberg et al22 found that the intravenous infusion of tempol decreases MAP in SHR by 32% and that NO synthase inhibitor abolishes the MAP response to tempol. Recent human studies have demonstrated that the constrictor actions of Ang II are enhanced during NO clamp and attenuated by vitamin C, which is a potent oxygen radical scavenger.12 Our data demonstrate that systemic and regional hemodynamic responses to tempol are markedly attenuated by pretreatment with the NO synthase inhibitor L-NAME. Thus, the results from the previous and present studies are consistent with the concept that stimulated oxygen radicals influence the vascular tone through the inactivation of NO. It was also reported that peroxynitrite, which is the chemical combination of superoxide with NO,34 oxidizes arachidonic acid and thus may stimulate the formation of a potent vasoconstrictor isoprostane.10,15,35 Other possibilities cannot be ruled out and need to be examined further.

In summary, the present study characterizes both systemic and regional hemodynamics in conscious Ang II–infused hypertensive rats. Chronic Ang II infusion produced a significant elevation in MAP associated with a significant increase in TPR and decrease in CO. The blood flow rates in the brain, spleen, large intestine, and skin were significantly reduced in Ang II–infused hypertensive rats compared with the vehicle-infused normotensive animals; however, the flow rates in the brain, lung, heart, liver, kidney, stomach, mesenterium, skeletal muscle, and testis were maintained. Ang II–infused hypertensive rats showed doubled vascular superoxide production, which was normalized by treatment with tempol. Tempol significantly reduced MAP and TPR, with no change in CO, in Ang II–infused rats, while having no effect on these parameters in vehicle-infused rats. In Ang II–infused rats, tempol did not alter the blood flow to any of the organ beds but significantly decreased vascular resistance in the brain, heart, liver, kidney, small intestine, and large intestine. Thus, not all organs and tissues did contribute equally to tempol-induced reduction in TPR in Ang II–infused hypertensive rats. We also observed that L-NAME markedly attenuated the systemic and regional hemodynamic responses to tempol. These results suggest that in this model of hypertension, oxidative stress may have contributed to the alterations in both systemic blood pressure and regional hemodynamic control through the inactivation of NO, at least in part.
Acknowledgments

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References

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