Exogenous L-Arginine Ameliorates Angiotensin II–Induced Hypertension and Renal Damage in Rats

Niwanthi W. Rajapakse, Carmen De Miguel, Satarupa Das, David L. Mattson

Abstract—Experiments were performed to determine whether exogenous L-arginine could ameliorate angiotensin II–induced hypertension and renal damage. Rats were instrumented with chronic indwelling femoral venous and arterial catheters for infusions of drugs and measurement of conscious arterial pressure. Arterial blood pressure significantly increased from 124±1 to 199±4 mm Hg, after 9 days of continuous infusion of angiotensin II (20 ng/kg per minute; IV; n=6 to 9). In contrast, the increase in arterial pressure after 9 days of angiotensin II infusion was significantly blunted by 45% (P=0.0003) in rats coadministered L-arginine (300 μg/kg per minute; IV; n=7 to 9). The glomerular injury index was significantly greater in rats administered angiotensin II in comparison with rats administered saline vehicle (P<0.001). Coinfusion of L-arginine significantly increased plasma nitrate/nitrite concentrations (P<0.001) and completely prevented angiotensin II–induced glomerular damage (P<0.001). Angiotensin II infusion alone and combined angiotensin II plus L-arginine infusion significantly increased urinary albumin excretion. Albuminuria in rats administered angiotensin II plus L-arginine is likely to be because of increased intraglomerular pressure. Our experiments demonstrate that L-arginine can blunt angiotensin II–induced hypertension and associated renal damage. This latter observation is most exciting because it indicates that increasing NO bioavailability, in addition to lowering arterial pressure, can greatly reduce hypertension-induced renal damage. (Hypertension. 2008;52:1084-1090.)

Key Words: hypertension ■ angiotensin II ■ L-arginine ■ NO ■ kidney

Angiotensin II is a potent vasoconstrictor and has been shown to cause hypertension when infused chronically into the systemic circulation.1,2 This model of hypertension closely mimics increased intrarenal angiotensin II formation, as well as high bioavailability of superoxide and low bioavailability of NO observed in human essential hypertension.3–5 Angiotensin II can stimulate the production of reactive oxygen species,6,7 which act as NO scavengers1,8 and uncouple NO synthase.1 Uncoupled NO synthase produces superoxide, creating a vicious cycle that further reduces NO bioavailability in hypertension. It has been suggested that reduced bioavailability of NO makes a major contribution to the development and maintenance of hypertension and, in particular, associated target organ damage and endothelial dysfunction.1,5,9,10 Thus, treatments that increase the bioavailability of NO should be able to interrupt the vicious cycle that maintains hypertension and associated end organ damage. In fact, there is evidence that antihypertensive treatments that increase NO bioavailability, as opposed to those that merely lower arterial pressure, exert additional beneficial effects to hypertensive patients, particularly in preventing target organ damage.9 Many recent studies have focused on strategies to reduce NO inactivation by superoxide as a means of increasing NO bioavailability in hypertension.6,8,11 Although the formation of NO equally affects its bioavailability, the potential beneficial effects of increasing NO formation in hypertension have received less attention.

L-Arginine is the substrate for vascular NO formation.12 The intracellular level of L-arginine (100 to 3800 μmol/L) in cultured endothelial cells13 far exceeds the Michaelis-Menten constant of NO synthase for L-arginine (<5 μmol/L).14 The “L-arginine paradox” is that endogenous NO formation depends on the extracellular L-arginine concentration despite the extremely high intracellular L-arginine levels.15–17 For example, in the isolated perfused kidney preparation, renal perfusion flow rate, glomerular filtration rate, urine flow, and sodium reabsorption all decreased when L-arginine was eliminated from the perfusate.18 In anesthetized Sprague-Dawley rats, L-arginine increased total renal blood flow,17 renal medullary perfusion, and NO content.15 The results of this latter study also indicated that infusion of amino acids that compete with L-arginine for cellular uptake reduced renal medullary perfusion and NO content in anesthetized rats.15 The data of these functional studies indicate that extracellular concentrations of L-arginine and the uptake mechanisms that transport L-arginine into intracellular compartments play important roles in modulating NO formation in the kidney under normal physiological conditions.
Under conditions of hypertension, increasing l-arginine concentration enhances NO-dependent vasorelaxation and other indices of endothelial function.\textsuperscript{19–24} For example, in Dahl salt-sensitive rats, chronic oral, intravenous, or medullary interstitial administration of l-arginine prevented sodium-dependent hypertension.\textsuperscript{20–23,25} L-Arginine has also been shown to be beneficial in reducing arterial pressure and improving endothelial function in essential hypertensive patients with mild-to-moderate hypertension.\textsuperscript{26,27} Together, these data indicate that l-arginine exerts beneficial effects in different forms of hypertension.

The aim of the current study was to determine whether exogenous l-arginine can interrupt the vicious cycle that reduces NO bioavailability in angiotensin II–induced hypertension. We hypothesized that exogenous l-arginine can increase the bioavailability of NO and ameliorate angiotensin II–dependent hypertension and kidney damage.

Methods

Animals

Forty-three male Sprague-Dawley rats weighing between 300 and 332 g were used in this study. The animals were purchased from Harlan Sprague Dawley (Madison, Wisc), and housed in the Medical College of Wisconsin Animal Resource Center. Rats were provided with food and water ad libitum. All of the experiments were conducted in accordance with the Medical College of Wisconsin Institutional Animal Care and Use Committee guidelines.

Surgical Preparations

Rats were deeply anesthetized with an IP injection of ketamine (35 mg/kg), xylazine (10 mg/kg), and acepromazine (0.5 mg/kg), with supplemental anesthesia administered as required. Catheters were placed in the femoral artery and vein as we described previously.\textsuperscript{28} After recovery from anesthesia, rats were placed in individual stainless steel cages, which permitted conscious blood pressure measurements (protocol 1) or blood and urine collection (protocol 2).

Protocol 1

After a 1-week recovery period, blood pressure was measured from 10 AM to 1 PM daily. After 3 days of control blood pressure measurements, rats were randomly divided into 3 groups. The first group of rats (n=6 to 9) received IV infusions of angiotensin II (20 ng/kg per minute) in saline vehicle (1 mL/h), and the second group of rats (n=7 to 9) received IV infusions of angiotensin II (Sigma Chemical Co; 20 ng/kg per minute) and l-arginine (Sigma Chemical Co; 300 mg/kg per minute). All of these infusions were continued for 9 days. The third group of rats (n=5) received IV infusions of angiotensin II (20 ng/kg per minute) only during the first 7 days. An IV infusion of l-arginine (300 mg/kg per minute) was also commenced on day 8. Both l-arginine and angiotensin II infusions were continued until day 15. This latter group of rats allowed us to determine whether l-arginine can reverse angiotensin II–induced hypertension.

Protocol 2

Rats were allowed a 1-week period to recover from surgery. At the end of week 1, rats were randomly divided into 3 treatment groups. The first group of rats received an IV infusion of saline vehicle (1 mL/h) only (n=6). The second group of rats received IV infusions of angiotensin II (20 ng/kg/min) and saline (n=7), whereas the third group of rats received IV infusions of angiotensin II (20 ng/kg per minute) plus l-arginine (300 mg/kg per minute; n=6). Urine samples were collected overnight from 4 PM to 8 AM on the day before infusions commenced and also on the ninth (ie, last) day of the infusions. Blood samples were also collected on these days. Urinary albumin was quantified with Albumin Blue 580 dye (Molecular Probes) and a fluorescent plate reader (FL600, Bio-Tek). The plasma samples were filtered and analyzed using a nitrate/nitrite fluorometric assay kit (Cayman). The plates were read in a Synergy HT Spectrometer, using an excitation wavelength of 360 to 340 nm and an emission wavelength of 460 to 440 nm. At the end of the ninth day of infusions, the kidneys were collected for histological analysis as described below.

Histological Analysis of Kidney Tissues

Rats were anesthetized with sodium pentobarbital (50 mg/kg IP). Kidney tissues were prepared as we described previously.\textsuperscript{28} A Nikon E-400 fitted with a spot insight camera was used to photograph the slides. Digital micrographs were taken at different magnifications. Thirty to 40 glomeruli per rat were evaluated using the semiquantitative index method of Raji et al\textsuperscript{29} and scored from 0 (best) to 4 (worst) on the basis of glomerulosclerosis and mesangial expansion, as we described previously.\textsuperscript{30,31}

Statistical Analysis

All of the data are presented as means±SEMs. Unpaired or paired t tests and 1- or 2-way repeated-measures ANOVAs with Tukey or Holm Sidak posthoc tests were used as appropriate to evaluate the effects of saline vehicle, angiotensin II, l-arginine, and combined angiotensin II plus l-arginine treatments.

Results

Protocol 1

Conscious Blood Pressure Measurements

Control mean arterial pressure (MAP; before administration of any drugs) averaged 124±1, 115±1, and 121±1 mm Hg in rats that subsequently received angiotensin II (20 ng/kg per minute; IV) only (group 1), angiotensin II plus l-arginine (300 μg/kg per minute; IV; group 2), and angiotensin II and then l-arginine (group 3), respectively. Basal MAP was higher in the group of rats that received angiotensin II only compared with the group of rats that received angiotensin II plus l-arginine (P=0.03). In the group of rats that were administered angiotensin II only, 9 days of continuous angiotensin II infusion increased MAP from 124±1 mm Hg to 199±4 mm Hg (P=0.005). In contrast, in the group of rats that were coadministered l-arginine, MAP only increased up to 149±1 mm Hg (P=0.005; Figure 1). During the last 5 days of the infusions, MAP increased by 62±4 mm Hg in the group of rats that received angiotensin II alone and by 34±1 mm Hg in the group of rats that received angiotensin II plus l-arginine. Coadministration of l-arginine blunted hypertension by 45% (P=0.0003). In the group of rats that were administered angiotensin II for 7 days, followed by angiotensin II plus l-arginine for an additional 8 days, MAP was significantly increased from control values of 121±1 to 170±1 mm Hg by angiotensin II (P=0.009). Subsequent coadministration of l-arginine for 8 days prevented a further increase in MAP (Figure 2).

Protocol 2

Effects of Angiotensin II and Combined Angiotensin II Plus L-Arginine Treatments on Glomerular Damage

When compared with the kidneys of rats administered saline vehicle, there was a significantly greater level of glomerular damage (represented by blue fibrotic tissue and collapsed capillary structure) in the kidneys of rats administered angiotensin II. However, confusion of l-arginine significantly and
visibly reduced blue fibrotic tissue formation and also improved the collapsed nature of capillary structures in the glomeruli (Figure 3).

The glomerular injury score was 0.8 ± 0.05 in rats administered saline vehicle (n = 5). The glomerular injury index was significantly greater in rats administered angiotensin II when compared with the glomeruli of rats administered saline vehicle (P < 0.001). Coinfusion of L-arginine significantly reduced the glomerular injury score (P < 0.001; Figure 4).

**Effects of Angiotensin II and Combined Angiotensin II Plus L-Arginine Treatments on Plasma Nitrate/Nitrite Concentrations**

Control plasma nitrate/nitrite concentrations in rats administered saline (n = 6), angiotensin II (n = 7), and combined angiotensin II plus L-arginine (n = 6) were 0.19 ± 0.02, 0.11 ± 0.02, and 0.16 ± 0.02 μmol/L, respectively. The control plasma nitrate/nitrite concentrations were not significantly different among the 3 treatment groups (P = 0.07). Saline or angiotensin II infusion had little effect on plasma nitrate/nitrite concentrations. In contrast, coinfusion of L-arginine

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**Figure 1.** Daily conscious MAP in Sprague-Dawley rats administered either angiotensin II (ANGII; 20 ng/kg per minute; IV; n = 6 to 9) or combined angiotensin II plus L-arginine (L-Arg; 300 μg/kg per minute; IV; n = 7 to 9) for 9 days. All of the infusions were administered into the femoral vein. Vertical line indicates the commencement of infusions. *P < 0.05 from the final control day; †P < 0.05 from the other group on the same day (2-way ANOVA followed by a Holm-Sidak posthoc test).

**Figure 2.** Daily conscious MAP in Sprague-Dawley rats administered angiotensin II (ANGII; 20 ng/kg per minute; IV; n = 6) alone during the first 7 days and subsequent L-arginine (L-Arg; 300 μg/kg per minute; IV; n = 7 to 9) for the remaining 8 days. All of the infusions were administered into the femoral vein. Vertical lines indicate the commencement of infusions. *P < 0.05 from the final control day (by 1-way ANOVA and Holm-Sidak test).

**Figure 3.** Light micrographs of glomeruli of the kidneys of Sprague-Dawley rats administered saline vehicle (1 mL/h; n = 6), angiotensin II (ANGII; 20 ng/kg per minute; n = 7), or combined angiotensin II plus L-arginine (L-Arg; 300 μg/kg per minute; n = 6) for 9 days. Glomerular sclerosis (blue fibrotic tissue and collapsed capillary structure) is present in the kidneys of rats administered angiotensin II. There is visibly less glomerular injury in rats coadministered L-arginine vs rats administered angiotensin II alone.

**Figure 4.** Effects of continuous infusion of saline vehicle (1 mL/h; n = 6), angiotensin II (ANGII; 20 ng/kg per minute; IV; n = 7), or angiotensin II plus L-arginine (L-Arg; 300 μg/kg per minute; n = 6) for 9 consecutive days on glomerular injury score. *P values indicate the outcomes of unpaired t tests.
Figure 5. Plasma nitrate/nitrite concentrations (µM) in Sprague Dawley rats before (□) and after (■) administration of saline vehicle (1 mL/h; n=6), angiotensin II (ANGII; 20 ng/kg per minute; n=7) or angiotensin II plus L-arginine (L-Arg; 300 µg/kg per minute; n=6). All of the infusions were administered into the femoral vein. P values indicate the outcomes of 2-way repeated-measures ANOVA with Tukey posthoc tests. *P<0.05 vs before treatment in the same group of rats. ¥P<0.05 vs rats administered angiotensin II.

Effects of Angiotensin II and Combined Angiotensin II Plus l-Arginine on Albumin Excretion

Albumin excretion, an index of kidney disease, is illustrated in Figure 6. Baseline albumin excretion before administration of any treatments averaged 8.7±6, 8.8±5.9, and 5.9±6.4 mg/d in rats that subsequently received saline vehicle (n=6), angiotensin II (n=7), or angiotensin II plus L-arginine (n=6), respectively. These baseline albumin excretion levels did not differ among the different treatment groups (P=0.5). Saline vehicle had little effect on urinary albumin excretion. In contrast, angiotensin II infusion significantly increased albumin excretion to 46±6 mg/d (P<0.001; Figure 5).

Table 1. Effects of infusion of saline vehicle (1 mL/h; n=6), angiotensin II (ANGII; 20 ng/kg per minute; n=7) and angiotensin II plus L-arginine (L-Arg; 300 µg/kg per minute; n=6) for 9 days on albumin excretion (mg/d) in Sprague-Dawley rats. All of the infusions were administered into the femoral vein. P values indicate the outcomes of 2-way repeated-measures ANOVA with Tukey posthoc tests. *P<0.05 vs before treatment in the same group of rats. ¥P<0.05 vs rats administered saline vehicle. □ Before treatment; ■ after treatment.

Discussion

Our study has a number of novel findings. First, our data demonstrate that exogenous L-arginine can significantly blunt angiotensin II–dependent hypertension and associated renal damage. This latter observation is most exciting because it stresses the importance of increasing NO bioavailability in addition to merely lowering arterial pressure in preventing hypertension-induced target organ damage. Second, our data provide evidence that, under conditions of hypertension, albuminuria can occur in the absence of significant glomerular damage. Third, our present data indicate that L-arginine infusion significantly increased plasma nitrate/nitrite levels, which is an index of plasma NO content. These data are in agreement with our previous data which indicate that exogenous L-arginine can increase endogenous NO levels. Finally, our present data indicate that

Figure 6. Effects of infusion of saline vehicle (1 mL/h; n=6), angiotensin II (ANGII; 20 ng/kg per minute; n=7) and angiotensin II plus L-arginine (L-Arg; 300 µg/kg per minute; n=6) for 9 days on albumin excretion (mg/d) in Sprague-Dawley rats. All of the infusions were administered into the femoral vein. P values indicate the outcomes of paired t tests. *P<0.05 vs before treatment in the same group of rats.

Figure 7. Effects of infusion of saline vehicle (1 mL/h; n=6), angiotensin II (ANGII; 20 ng/kg per minute; n=7), and angiotensin II plus L-arginine (L-Arg; 300 µg/kg per minute; n=6) for 9 days on creatinine excretion (mL/min) in Sprague-Dawley rats. All of the infusions were administered into the femoral vein. P values indicate the outcomes of paired t tests.

Effects of Angiotensin II and Combined Angiotensin II Plus L-Arginine on Creatinine Clearance (as an Index of Glomerular Filtration Rate)

Creatinine clearance, as an index of glomerular filtration rate, is illustrated in Figure 7. Baseline creatinine excretion levels before administration of any treatments averaged 3±1, 4±1, and 3±1 mL/min in rats that subsequently received saline vehicle (n=6), angiotensin II (n=7), or angiotensin II plus L-arginine (n=6), respectively. The baseline creatinine clearance levels did not differ between different treatment groups (P=0.17). Saline vehicle, angiotensin II, and angiotensin II plus L-arginine had little effect on creatinine excretion levels (P≥0.16; Figure 7).
L-arginine can halt the development of angiotensin II–induced hypertension.

Our current study indicates that L-arginine can increase NO bioavailability during chronic angiotensin II infusion. We have shown previously that L-arginine can increase renal NO bioavailability under normal physiological conditions and that manipulation of L-arginine transport mechanisms result in alterations in NO levels in rats. Collectively, these data indicate that cellular L-arginine transport is an important determinant of endogenous NO bioavailability. This is paradoxical, because the Michaelis-Menten constant of NO synthase for L-arginine is <5 μmol/L and the intracellular L-arginine concentrations are in the range of 100 to 3800 μmol/L in cultured endothelial cells. However, the Michaelis-Menten constant of NO synthase for L-arginine under in vivo conditions is unknown but is likely to be much higher than demonstrated from the in vitro experiments. The presence of endogenous NO synthase inhibitors and compartmentalization of intracellular L-arginine pools are likely to increase the Michaelis-Menten constant of NO synthase for L-arginine under in vivo conditions. This could at least in part explain our observation that exogenous L-arginine increased endogenous NO bioavailability.

Our current data indicate that L-arginine can ameliorate angiotensin II–induced hypertension and related renal damage. We did not examine the effects of other amino acids that are not precursors to NO production in this model of hypertension. However, we have shown previously that chronic infusion of L-lysine or L-ornithine reduced renal NO bioavailability and initiated hypertension, whereas L-arginine attenuated these effects in Sprague-Dawley rats. This indicates that amino acids that are not precursors to NO production do not have the same effect on long-term blood pressure control as L-arginine.

Because the kidney plays an important role in angiotensin II–induced hypertension, the antihypertensive effects of L-arginine are likely mediated at least partly within the kidney. It has been shown that angiotensin II receptors in the kidney are obligatory for the development of hypertension in the angiotensin II–induced hypertension model. In addition, the pressure-natriuresis mechanism is shifted to the right (greater levels of arterial pressure) in all of the forms of hypertension studied to date, and all of the antihypertensive treatments must shift the pressure-natriuresis mechanism to the left (lower levels of arterial pressure) to ameliorate hypertension chronically. In fact, there is evidence that NO can shift the pressure-natriuresis mechanism to the left. Because our data indicate that L-arginine can increase NO production, it is likely that L-arginine shifts the pressure-natriuresis mechanism to the left by increasing NO bioavailability. It is doubtful that angiotensin II–dependent hypertension is mediated by angiotensin II–induced vasoconstriction in the systemic circulation, because if the pressure-natriuresis mechanism remains unaltered, then this would reduce arterial pressure by reducing the extracellular fluid volume.

Kidney tissue damage (as indicated by the glomerular injury index) in rats administered angiotensin II was significantly higher than in rats administered saline vehicle. Coinfusion of L-arginine completely prevented angiotensin II–dependent glomerular damage, despite the fact that arterial pressure in these animals was still well above the levels of normotensive rats (∼150 mm Hg). This intriguing observation indicates that L-arginine can prevent glomerular damage under conditions of hypertension. There is evidence that antihypertensive treatments that also increase NO bioavailability exert additional beneficial effects to hypertensive patients, particularly in preventing target organ damage. Our current data are in strong agreement with this notion and provide support for the use of L-arginine as an adjunct to current antihypertensive treatments. L-Arginine did not significantly blunt angiotensin II–induced increases in albumin excretion. At first glance, this seems to be at odds with our histological data. Under conditions of hypertension, albuminuria is caused by 2 main factors: increased intraglomerular pressure and glomerular injury. This latter factor is likely to be related to endothelial dysfunction, which occurs as a consequence of low NO bioavailability observed in hypertension. Because L-arginine significantly increased NO levels in rats administered angiotensin II, it is likely that this treatment improved endothelial dysfunction and thereby prevented glomerular damage in these rats. However, L-arginine blunted angiotensin II–induced hypertension by only 45%, and MAP of rats administered L-arginine plus angiotensin II was still ∼150 mm Hg. Thus, increased intraglomerular pressure (but not glomerular damage) must have contributed to albuminuria observed in these rats. Also, L-arginine can increase urinary albumin excretion independent of parallel increases in glomerular filtration rate, potentially by reducing proximal tubular protein reabsorption. In this regard, we are not surprised that L-arginine was able to completely prevent glomerular damage but was unable to significantly blunt albuminuria. Regardless, of the mechanism(s) responsible for albuminuria in rats administered angiotensin II plus L-arginine, our data provide evidence that albuminuria can occur under conditions of hypertension, in the absence of significant glomerular damage.

Our data indicate that L-arginine can halt but not reverse angiotensin II–induced hypertension. However, it should be noted that, even in the group of rats that simultaneously received angiotensin II plus L-arginine, ∼5 days of chronic L-arginine infusion was required before an effect of L-arginine on blood pressure could be observed (Figure 1). Thus, it is likely that, in the group of rats that received angiotensin II and then L-arginine, the effects of L-arginine did not start to have an effect until 5 days after commencement of this infusion. In fact, blood pressure continued to increase within the first 4 days after commencement of L-arginine, reaching a maximum of 184 mm Hg on day 15 (Figure 2). This increase in blood pressure likely reflects the predominating effects of angiotensin II during this period. The reduction in blood pressure from day 16 is likely to reflect the effects of L-arginine. These data provide evidence that L-arginine has the potential to reverse established hypertension.

Chronic angiotensin II infusion has been shown to increase endothelin and superoxide levels. This is suggested to largely contribute to the systemic and renal effects observed during chronic angiotensin II infusion. Reactive oxygen...
species can scavenge NO and uncouple NO synthase.\textsuperscript{1,3} Under these conditions, NO synthase will not produce NO but will rather produce superoxide, creating a vicious cycle that further reduces NO.\textsuperscript{3} Low bioavailability of NO has been suggested to play a major role in maintaining hypertension and the development of associated target organ damage.\textsuperscript{9} Therefore, a treatment regimen that interrupts the vicious cycle that reduces NO bioavailability in hypertension should, in turn, be able to ameliorate hypertension and prevent associated target organ damage. It has been shown previously that administration of the superoxide dismutase mimetic Tempol\textsuperscript{44} reduced superoxide bioavailability and ameliorated hypertension induced by chronic angiotensin II infusion. Although these authors did not measure NO content, it is likely that the effects of Tempol were dependent on increased NO bioavailability.

Perspectives

We speculate that L-arginine inhibits the cascade of events that creates the vicious cycle leading to low NO bioavailability in hypertension, upstream to angiotensin II–induced superoxide formation. There is evidence that L-arginine has antioxidant properties.\textsuperscript{45,46} It has been shown that L-arginine can counteract high-salt diet–induced increases in the expression of NADPH subunits gp91phox and p47phox, as well as thromboxane B2 excretion.\textsuperscript{45} It is suggested that L-arginine can increase NO formation under conditions of increased superoxide bioavailability (such as under conditions of hypertension) by 3 mechanisms. First, L-arginine can increase NO formation via the conventional pathway by intact NO synthase. This mechanism is well supported by recent studies.\textsuperscript{15–17} Second, there is evidence that L-arginine can “re-couple” the uncoupled NO synthase.\textsuperscript{46} Finally, there is evidence that L-arginine can produce NO via a nonenzymatic pathway by reacting with reactive oxygen species.\textsuperscript{47} All of these actions should increase NO bioavailability under conditions of hypertension. Our current results do not allow us to directly determine the effects of L-arginine on superoxide production. We speculate that L-arginine reduces superoxide bioavailability by increasing the bioavailability of NO. However, we cannot completely exclude the possibility that antihypertensive and renoprotective effects of L-arginine might be partly mediated by NO–independent pathways. This hypothesis merits investigation in the future.

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Disclosures

None.

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