Epoxyeicosatrienoic Acid–Mediated Renal Vasodilation to Arachidonic Acid Is Enhanced in SHR

Silvia I. Pomposiello, Mairead A. Carroll, John R. Falck, John C. McGiff

Abstract—We tested the hypothesis that cyclooxygenase-independent vasodilation produced by arachidonic acid (AA) is mediated by epoxyeicosatrienoic acids (EETs) and is blunted in the spontaneously hypertensive rat (SHR). At normal perfusion pressure (PP; 70 to 90 mm Hg), AA constricted the renal vasculature in both SHR and normotensive Wistar-Kyoto rats, an effect abolished by cyclooxygenase inhibition, and converted to vasodilation when PP was raised to ≈200 mm Hg. Unexpectedly, renal vasodilation elicited by AA was greater in the SHR at high PP; for example, 2.5, 5, and 10 µg of AA produced PP declines of 54±9, 92±10, and 112±5 mm Hg, respectively, in SHR compared with 26±3, 45±5, and 77±6 mm Hg in Wistar-Kyoto rats (P<0.01). However, the renal vasodilator responses to acetylcholine (0.1 µg) and sodium nitroprusside (1 µg) did not differ between strains, indicating that vascular responsiveness to AA was independent of intrinsic changes in vascular smooth muscle. Hyperresponsiveness of the renal vasculature to AA may be unique for the SHR, because it did not occur in Sprague-Dawley rats with angiotensin II–induced hypertension. 5,8,11,14-Eicosatetraynoic acid (ETYA; 4 µmol/L), an inhibitor of all AA pathways, attenuated the vasodilator responses to AA, as did treatment with stannous chloride, which depletes cytochrome P450 enzymes, suggesting that a cytochrome P450 AA metabolite mediated the renal vasodilation. N-Methylsulfonfyl-12,12-dibromododec-11-en-amine (DDMS; 2 µmol/L), a selective ω-hydroxylase inhibitor, did not affect AA-induced vasodilation, whereas selective inhibition of epoxygenases with either miconazole (0.3 µmol/L) or N-methylsulfonfyl-6-(2-propargyloxyphenyl) hexanamide (MS-PPOH; 12 µmol/L) did, indicating that one or more EETs were involved in the renal vasodilator action of AA at high PP. This conclusion was supported by the demonstration that AA greatly enhanced the renal efflux of EETs at high PP but not at basal PP. (Hypertension. 2001;37:887-893.)

Key Words: hypertension, renal ■ kidney ■ arachidonic acid ■ vasodilation

Cytochrome P450 (CYP)-dependent metabolism of arachidonic acid (AA), the designated “third” pathway of the AA cascade,1 generates products that are vasoactive and participate in the regulation of extracellular fluid volume, properties that signify a role for CYP AA metabolites in the control of blood pressure.2-5 The products of CYP-catalyzed AA metabolism are hydroxyeicosatetraenoic acids (HETEs); chiefly 20-HETE and epoxyeicosatrienoic acids (EETs), the latter metabolized by epoxide hydrolase to form the corresponding dihydroxyeicosatrienoic acids (DHETs).1,2

In the first study that linked CYP AA metabolites to blood pressure regulation, Sacerdoti and colleagues6 used stannous chloride (SnCl2), an inducer of heme oxygenase, to deplete CYP enzymes, which prevented the development of hypertension in young spontaneously hypertensive rats (SHR). SnCl2 treatment did not, however, affect blood pressure in either normotensive rats or the adult SHR. 20-HETE, a product of CYP ω-hydroxylase, is the prohypertensive CYP AA metabolite par excellence by virtue of its vasoconstrictor potency and copious production by the renal vasculature.7-9 20-HETE is the principal product of preglomerular microvessels, at which site it is generated in increased amounts in the SHR vis-à-vis normotensive Wistar-Kyoto rats (WKY).10 Increased production of 20-HETE by the afferent arteriole is considered to be responsible for a rightward shift in the pressure-natriuresis curve, the hallmark of hypertension.10 Additional evidence for the importance of increased ω-hydroxylase activity and production of 20-HETE in the genesis of hypertension is based on the blood pressure–lowering ability in the young SHR of 1-aminozonbztiazole, a selective inhibitor of ω-hydroxylase.11 Further, treatment of (normotensive versus SHR) rats with CYP 4A antisense oligonucleotides also decreased renal synthesis of 20-HETE accompanied by reduced blood pressure in the young SHR.12 The cumulative import of these studies provides compelling support for a prohypertensive role for 20-HETE in the SHR.

Equally compelling studies by Makita and associates13 indicate an antihypertensive role for CYP-derived arachidionate EETs; indeed, a deficiency of EETs renders the rat liable to blood pressure elevation in response to increased dietary...
salt. Most recently, CYP 2C23 has been identified in the rat kidney as the major 2C arachidonate epoxygenase and the specific isoform of the 2C family that is subject to regulation by dietary salt. Salt sensitivity, as defined by blood pressure elevation in response to dietary salt loading, therefore, can be produced by deletion or inhibition of the 2C23 epoxygenase isoform. The EETs may also operate in a regulatory vascular mechanism that opposes the renal actions of 20-HETE at critical sites such as the afferent arteriole. In a recent study, Imig et al identified an epoxide-dependent vasodilator mechanism that antagonizes 20-HETE–induced constriction of the afferent arteriole. A quiescent CYP-dependent vasodilator system has been identified in the normotensive rat kidney, which became evident only after inhibition of cyclooxygenase (COX) and elevation of renal perfusion pressure (PP). These conditions resulted in the transformation of renal vasoconstriction produced by AA to vasodilation and was dependent on an intact endothelium. Further, the AA-induced renal vasodilation was inhibited by blockade of CYP AA metabolism. The present study was designed to examine expression of CYP-dependent AA vasodilation in the SHR vis-à-vis WKY as well as in another hypertensive model, angiotensin (AII)-induced hypertension. The working hypothesis was that normotensive rats would exhibit a more active CYP-dependent renal vasodilator mechanism than the SHR. However, this hypothesis was not validated because the renal vasodilator response to AA mediated by an EET was greater in SHR than in WKY.

**Methods**

**Materials**

Indomethacin, phenylephrine, acetylcholine (Ach), sodium nitroprusside (SNP), miconazole, and inorganic salts were purchased from Sigma. 5,8,11,14-Eicosatetraynoic acid (ETYA) was purchased from Nuchek and sodium arachidonate was obtained from Biomol. Sodium arachidonate was obtained from Nuchek and human ALL from American Peptide Company Inc. N-Methylsulfonlyl-12,12-dibromodec-11-en-amide (DDMS) and N-methylsulfonlyl-6-(2-propargyloxyphenyl) hexanamide (MS-PPOH) were provided by Dr. J.R. Falcó (University of Texas, Southwestern Medical Center, Dallas). Indomethacin was dissolved in 4.2% NaHCO3, ETYA in Na2CO3 (50 mmol/L) and miconazole, and DDMS and MS-PPOH in ethanol. Sodium arachidonate was dissolved in distilled water, divided into 1-mg/mL aliquots, and stored under N2 at −70°C.

**Animals**

Male SHR, WKY, and Sprague-Dawley rats (SD) (Charles River Laboratory, Wilmington, Mass), 13 to 15 weeks of age were used for experiments. The AII-induced model of hypertension was induced with a 19-gauge needle and perfused in situ at constant flow by a Watson Marlow pump (model 505S) with warmed (37°C) and gassed (95% O2–5% CO2) Krebs-Henseleit solution (in mmol/L): NaCl (118), KCl (4.7), KH2PO4 (1.19), MgSO4 (1.19), CaCl2 (1.9), NaHCO3 (25), and glucose (5.5). PP was measured with a Harvard Apparatus pressure transducer and recorded on a Soltect (model 1244) chart recorder. In those preparations in which the renal effluent was collected, the kidney was removed after arterial cannulation and suspended in a water-jacketed organ bath at 37°C.

**Protocol I: Renal Vascular Effect of AA**

A bolus injection of AA (2.5 μg) was administered as a bolus injection into the renal artery before and after treatment with indomethacin (10 μmol/L) for 30 minutes. Phenylephrine (0.5 to 1×10−6 mol/L) was then added to the perfusate to increase PP to ~200 mm Hg. A dose-response curve to AA (1 to 10 μg) and bolus injections of Ach (0.1 μg) or SNP (1 μg) were compared for SHR and WKY or SD infused with AII and sham control rats.

**Protocol II: Role of CYP Metabolites in Vasodilation Induced by AA**

All experiments were performed at ~200 mm Hg PP in the presence of indomethacin (10 μmol/L). First, we studied the effect of the ETYA (4 μmol/L) on the vascular response to AA. To assess a CYP component of the AA-induced vasodilation, animals were treated for 4 days with SnCl2 (10 mg/100 g body wt SC), which induces heme oxygenase, an enzyme that metabolizes heme and reduces its availability for CYP, causing depletion of renal CYP. After treatment with either SnCl2 or vehicle, vascular responses to AA (1 to 10 μg) and Ach (0.1 μg) or SNP (1 μg) were determined and compared with those from kidneys of vehicle-treated animals.

To define further the contribution of CYP AA metabolites to the renal vascular effect of AA, experiments were performed with newly developed specific CYP inhibitors that allow discrimination between hydroxylase and epoxygenase activity. DDMS (2 μmol/L) was used to inhibit ω-hydroxylation; miconazole (0.3 μmol/L) and MS-PPOH (12 μmol/L) were used to selectively inhibit the epoxygenase pathway. Dose-response curves to AA (1 to 10 μg) were determined and bolus injections of either Ach (0.1 μg) or SNP (1 μg) were compared with those from vehicle-treated kidneys.

**Protocol III: Release of CYP Metabolites**

The unseparated ureteral and venous effluents were collected for 5 minutes before and after a bolus injection of AA (5 μg). To measured volumes of renal perfusates, 5 ng of 20-HETE-d3 plus 7.5 ng of a mix of EET-d6 (8,9-, 11,12-, and 14,15-EET) were added as internal standards. The eicosanoids were extracted and separated by high-performance liquid chromatography and derivatized and analyzed by gas chromatography–mass spectrometry as described previously.

**Statistical Analysis**

Results are expressed as mean±SEM. A student’s 2-sample t test or a Wilcoxon 2-sample rank sum test was used to analyze differences between groups, depending on whether assumptions of normality were met. A value of P<0.05 was considered significant.

**Results**

**Protocol I: Renal Vascular Effect of AA**

Kidneys of SHR and WKY were perfused in situ with Krebs-Henseleit solution at 7 to 10 mL/min to achieve a basal PP of 70 to 90 mm Hg. A bolus injection of AA (2.5 μg) constricted the renal vasculature in both SHR and WKY, which was abolished by COX inhibition with 10 μmol/L indomethacin (Figure 1). However, when renal PP was increased by phenylephrine to ~200 mm Hg, AA produced vasodilation followed by vasoconstriction (Figure 2a). The
Vasoconstriction was blocked by COX inhibition, whereas the vasodilator action of AA persisted (Figure 2b). Unexpectedly, in rat kidneys subject to high PP and treated with indomethacin, the decrease in PP elicited by AA and bradykinin was enhanced in SHR compared with WKY (Figure 3). The renal endothelium-dependent vasodilator effect of Ach and the endothelium-independent vasodilator effect of SNP did not differ between SHR and WKY, indicating that relaxation of renal blood vessels to standard vasodilator agents was unimpaired (Figure 3 and Table).

We obtained additional evidence that the SHR had an exaggerated renal vasodilator response to AA when compared with another normotensive rat strain. The renal vasodilator responses of SD to the lower doses of AA (1 and 2.5 μg) were indistinguishable from those of WKY, whereas at the higher doses of AA (5 and 10 μg), AA-induced vasodilation was less in SD than in WKY; for example, to 5 μg AA, 25 ± 7, 45 ± 5, and 92 ± 6 mm Hg decreases in renal PP occurred, and to 10 μg of AA, 44 ± 6, 77 ± 6, and 112 ± 5 mm Hg decreases were observed. The increase in PP elicited by 2.5 μg AA was 66 ± 10 mm Hg in WKY and 44 ± 6 mm Hg in SHR. Results are expressed as mean ± SEM.

Figure 1. a, Indomethacin (10 μmol/L) inhibits vasoconstriction induced by AA (2.5 μg) in isolated perfused kidneys of WKY and SHR at PP ~80 mm Hg. b, ΔPP = change in renal PP produced by 2.5 μg AA. Results expressed as mean ± SEM (n = 4).

Figure 2. Representative traces of vascular responses to AA (2.5 to 10 μg), bradykinin (BK; 0.1 μg), Ach (0.1 μg), and SNP (1 μg) in SHR isolated perfused kidneys constricted with phenylephrine (5 × 10⁻⁷ mol/L) at PP ~200 mm Hg. Experiments were conducted without (a) and with (b) indomethacin (10 μmol/L).

Figure 3. Comparison of vasodilator responses to AA (1 to 10 μg), bradykinin (BK; 0.1 μg), Ach (0.1 μg), and SNP (1 μg) in SHR and WKY isolated perfused kidneys constricted to ~200 mm Hg with phenylephrine (5 × 10⁻⁷ mol/L). Indomethacin (10 μmol/L) was present throughout experiment. Results are expressed as mean ± SEM. (n = 5 to 6). *P < 0.01, **P < 0.005, SHR vs WKY.
 decreases in renal PP occurred for SD, WKY, and SHR, respectively. In contrast to the exaggerated vasodilator response to AA in SHR, in the AII hypertension model, renal vasodilation produced by AA was either eliminated or greatly diminished (Figure 4).

**Protocol II: Role of CYP Metabolites in Vasodilation Induced by AA**

In phenylephrine-preconstricted kidneys pretreated with the COX inhibitor indomethacin, ETYA (4 \( \mu \text{mol/L} \)), an inhibitor of all AA pathways, significantly diminished the vasodilator response to AA in both the SHR and WKY (Figure 5a), as did depletion of CYP enzymes in vivo by inducing heme oxygenase activity with SnCl₂ (Figure 5b), indicating that a CYP product of AA metabolism was a likely candidate for the augmented response in the SHR. Having uncovered a non-COX, eicosanoid-dependent renal vasodilator mechanism that was operative at high renal PP, we next examined potential CYP AA products that could mediate the renal vasodilation. Identification of a CYP AA metabolite as a mediator of the renal vasodilation to AA made use of highly specific inhibitors that readily distinguish the participation of an EET from that of a HETE.\(^9\) DDMS (2 \( \mu \text{mol/L} \)), the \( \omega \)-hydroxylase inhibitor, did not affect AA-induced vasodilation, thereby eliminating 20-HETE as a potential mediator (Figure 6). However, selective inhibition of epoxygenases with either miconazole (0.3 \( \mu \text{mol/L} \)) or MS-PPOH (12 \( \mu \text{mol/L} \)) greatly reduced the AA response (Figure 7, a and b). Importantly, none of the inhibitors affected endothelium-dependent (Ach) and endothelium-independent (SNP) renal vasodilator responses (Table), indicating that altered relaxation of the renal vasculature produced by CYP inhibition was independent of intrinsic changes in either the endothelium or vascular smooth muscle.

**Protocol III: Release of CYP Metabolites**

At basal PP, AA (5 \( \mu \text{g} \)) did not induce efflux of either EETs or 20-HETE in SHR and WKY (Figure 8). At high PP, AA induced a 3-fold increase in renal efflux of EETs in both SHR and WKY but was without effect on 20-HETE release. A sharp decline in efflux of EETs occurred in the SHR when PP was elevated \( (P<0.06) \). Nevertheless, the SHR and WKY did not differ in the magnitude of EETs released by AA. Interestingly, at basal PP, renal efflux of 20-HETE was greater in SHR than in WKY. In the SHR, at high PP, the release of 20-HETE in response to AA was reduced by 35% in SHR \( (P<0.05) \) compared with release at basal PP (Figure 8). This stands in contrast to the severalfold elevation of EET efflux produced by AA at high PP in SHR.

**Discussion**

Our principal findings are 3-fold: (1) At elevated renal PP, the COX-independent renal vasodilator response to AA of the SHR is enhanced compared with that of the WKY. (2) An EET is the candidate mediator of AA-induced renal vasodilation in both SHR and WKY as well as in the augmented AA response in the SHR based on (a) marked attenuation of AA-induced vasodilation in response to selective inhibition of epoxygenases and (b) the surge in EET efflux from the kidney that occurs coincident with the renal vasodilator
response to AA. (3) 20-HETE release from the kidney is unaffected by AA and is reduced by high PP conditions. The relative contribution of tubular fluid and renal venous efflux to the levels of CYP AA was not determined. Our previous study in the rabbit isolated kidney indicated that tubular fluid made the major contribution to total CYP AA metabolites measured in the combined effluents.21

This study issued directly from our previous study, which uncovered a dormant vasodilator response to AA in the rat kidney requiring inhibition of COX and elevation of renal PP to be demonstrated and was mediated by a CYP AA metabolite.16 Thus, at low renal PP (≈80 mm Hg), the renal vasoconstrictor response to AA in both SHR and WKY was abolished when the production of vasoconstrictor prostanoids was blocked with indomethacin.16 Elevation of renal PP to ≈200 mm Hg after inhibition of COX unmasked a vasodilator response to AA that was mediated by a CYP-dependent metabolite of AA. Although an imbalance between vasopressor and vasodepressor agents, in favor of the former, have been identified in various diseases states, including hypertension,9 the findings of our study appear to be an exception to this generalization because the magnitude of the renal vaso-

Figure 5. Effects of ETYA (4 μmol/L), an inhibitor of all AA metabolic pathways (a), and SnCl₂ (10 mg/100 g per day for 4 days) (b), which depletes renal CYP enzymes on vasodilation induced by AA (0.25 to 10 μg) in SHR and WKY isolated perfused kidneys constricted to ≈200 mm Hg with phenylephrine (5×10⁻⁶ mol/L). Indomethacin (Indo, 10 μmol/L) was present throughout experiment. Results are expressed as mean±SEM (n=4). *P<0.05, **P<0.01, †P<0.005, ††P<0.001, treatment vs control.

Figure 6. Effect of DDMS (2 μmol/L), the ω/ω-1 hydroxylase inhibitor, on vasodilation induced by AA (0.25 to 10 μg) in SHR and WKY isolated perfused kidneys constricted to ≈200 mm Hg with phenylephrine (5×10⁻⁶ mol/L). Indomethacin (Indo, 10 μmol/L) was present throughout experiment. Results are expressed as mean±SEM (n=4).

Figure 7. Effect of selective epoxygenase inhibitors: a, miconazole (0.3 μmol/L), or b, MS-PPOH (12 μmol/L), on vasodilation induced by AA (0.25 to 10 μg) in SHR and WKY isolated perfused kidneys constricted to ≈200 mm Hg with phenylephrine (5×10⁻⁶ mol/L) and treated with indomethacin (Indo, 10 μmol/L). Results are expressed as mean±SEM (n=4 to 5). *P<0.05, **P<0.01, †P<0.005, miconazole or MS-PPOH vs control.
has been confirmed in the present study. To determine whether the COX-independent hyperresponsiveness to AA is unique for the SHR, we examined the effect of AA on a different experimental model of hypertension, AIH-induced hypertension.17 In contrast to our findings in the SHR, renal vasodilatation produced by AA was greatly diminished in this hypertensive model when compared with normotensive SD.

A potentially important relation between blood pressure elevation and renal 20-HETE production was also suggested by the decline (~35%) in 20-HETE release when renal PP was abruptly increased from 80 to 200 mm Hg. This is the first direct demonstration that renal production/release of the prohypertensive 20-HETE may be subject to regulation by renal PP, suggesting the operation of a mechanism that moderates production of 20-HETE. At basal renal PP, AA neither increased renal release of EETs nor produced renal vasodilation. In contrast, when PP was elevated, AA increased EET release from the kidney, whereas efflux of 20-HETE was unaffected. The failure for AA to promote efflux of 20-HETE irrespective of PP levels, and in both SHR and WKY, is puzzling. Whether a receptor-mediated release of 20-HETE, such as in response to either AII or ET-1 is also affected,8,20 has yet to be determined and should shed light on endogenous versus exogenous sources of AA as determinants of vascular responsiveness. A cause-and-effect relation between EET release and AA-induced renal vasodilation at high PP is likely because inhibition of epoxyenase was associated with prevention of the vasodilator effect of AA. These findings support the general conclusion, based on selective inhibition of epoxyenases, that an EET(s) mediated the renal vasodilator effect of AA when renal PP was elevated. Neither the vasodilator response to Ach, which is endothelium-dependent, nor vasodilation produced by SNP, a nitric oxide donor, which is endothelium-independent, was affected by inhibition of CYP enzymes, indicating that the CYP inhibitors did not have a direct effect on reactivity of the renal vasculature to vasodilator agents.

A countervailing mechanism that promotes production of an antihypertensive CYP AA metabolite is suggested by the ability of administered AA to increase renal EET release only when renal PP was elevated. However, a deficiency in renal EET production by the SHR was apparently uncovered by the sharp decline in EET efflux occasioned by elevating renal PP, suggesting deficient pressure-induced biosynthesis of vasodilator EETs in the SHR. Because exogenous AA produced similar renal efflux of EETs in SHR and WKY at high PP, an abnormality in phospholipase activity may be responsible for the failure of the SHR to respond to high PP by increasing EET production from endogenous AA.

It is instructive to review these findings in terms of the important findings of Imig et al10 regarding the hormonal basis for resetting the pressure-natriuresis relation in the SHR by enhancing tone of the prepglomerular microvessels through increased renal production of 20-HETE. On the other hand, WKY demonstrated the reverse; namely, production of the 11,12-epoxide exceeded that of 20-HETE. Imig et al15 examined changes in the production of 20-HETE and an EET for effects on the diameter of that vascular segment primarily responsible for producing changes in renal vascular resistance (RVR), the afferent glomerular arteriole. The identity of the epoxide was presumed to be 11,12-EET because it is the most potent dilator of the major resistance blood vessel,24 the afferent glomerular arteriole, and is the principal epoxide produced by the kidney (and by prepglomerular microvessels).2 When renal PP was elevated, the afferent arteriole constricted by increasing production of 20-HETE, an effect that was (1) potentiated by inhibiting production of EETs, which antagonize the vasoconstrictor action of 20-HETE, and (2) attenuated by inhibiting formation of 20-HETE. As in the study of Imig et al,15 we found that an EET reduced RVR.

The augmented renal vasodilator effect of AA in SHR versus WKY could not be accounted for by increased renal EET released by AA in the SHR because similar increases in renal EET efflux occurred in both SHR and WKY. However, there are several factors regarding production and metabolism of EETs that have not been addressed in the present study and may have contributed to the greater renal vasodilator responsiveness of SHR versus WKY: (1) Increased production of an individual epoxide could not have been detected because only total EETs were measured. Of the EETs, the 5,6-EET has

Figure 8. Renal efflux of total EETs (left) and 20-HETE (right) before and after stimulation with AA (5 μg) in SHR and WKY isolated perfused kidneys under basal PP (70 to 90 mm Hg) and after elevation of PP (200 mm Hg) with phenylephrine (8×10−7 mol/L). Indomethacin (10 μmol/L) was present throughout experiment. Results are expressed as mean±SEM (n=4), *P<0.05, AA vs either control or SHR vs WKY.
been reported to be the most potent dilator of the renal vasculature of SHR and to be selectively increased in SHR. The functional implications of these findings regarding a renal vasodilator system mediated by an EET must await further studies in conscious rats conducted over longer intervals and subject to variable experimental conditions such as changes in dietary salt. Whether or not the renal vascular mechanism mediated by an EET is an important component of anti-hypertensive defenses deserves serious consideration. Recent studies have identified arachidonate epoxides as endothelium-derived hyperpolarizing factors at several sites in the vasculature and underscore the potential importance of this area of research to circulatory regulation. The relation between endothelium-derived hyperpolarizing factors and arachidonate epoxides is approaching resolution. Additional factors that possibly operate in SHR to account for AA renal vascular hyperresponsiveness include density of EET receptors that have recently been suggested to operate through a G protein-mediated mechanism; enhanced activity of Gs coupled responses of KCa channels; sensitivity of the target site, the KCa channel; and other components of EET-initiated cell signaling events such as efficiency of ADP-ribosylation of Gs and enhanced responsiveness to signaling molecules effecting Ca2+ entry/mobilization.

The functional implications of these findings regarding a renal vasodilator system mediated by an EET must await further studies in conscious rats conducted over longer intervals and subject to variable experimental conditions such as changes in dietary salt. Whether or not the renal vascular mechanism mediated by an EET is an important component of anti-hypertensive defenses deserves serious consideration. Recent studies have identified arachidonate epoxides as endothelium-derived hyperpolarizing factors at several sites in the vasculature and underscore the potential importance of this area of research to circulatory regulation. The relation between endothelium-derived hyperpolarizing factors and arachidonate epoxides is approaching resolution.

Acknowledgments
This research was supported in part by grants from the National Institutes of Health (HL-343000 and HL-25394). We wish to acknowledge the excellent technical assistance provided by Jessica Gallman and to thank Dr John Quilley for his helpful suggestions and Barbara Stern for editorial assistance in preparing the manuscript.

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Hypertension. 2001;37:887-893
doi: 10.1161/01.HYP.37.3.887

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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