Potential Roles of Angiotensin Receptor–Activating Autoantibody in the Pathophysiology of Preeclampsia

Yang Xia, Susan M. Ramin, Rodney E. Kellems

Preeclampsia affects ~7% of first pregnancies and is one of the leading causes of maternal and neonatal mortality and morbidity in the United States and the world. The clinical hallmarks of the disorder include hypertension, proteinuria, hypercoagulability, edema, and placental abnormalities. In advanced stages, clinical symptoms include cerebral edema, renal failure, and the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. The clinical management of preeclampsia is hampered by the lack of reliable diagnostic tests and effective therapy for the disorder. In some cases, termination of pregnancy is the only available option to prevent further deterioration of the fetus and mother. Fifteen percent of all preterm births are indicated early deliveries for preeclampsia. The resulting preterm births and the associated increased infant morbidity and mortality are especially disheartening consequences of preeclampsia.

Despite being one of the leading causes of maternal death and a major contributor to maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia are poorly understood. Roberts and colleagues were among the first to propose that alterations in endothelial cell function by activating agents produced by the placenta initiate the clinical syndromes of preeclampsia. Circulating factors, such as inflammatory cytokines, endothelin, and soluble vascular endothelial growth factor receptor termed soluble fms-like tyrosine kinase-1 (sFlt-1), are elevated in preeclamptic women and are proposed to be important links between placental ischemia and endothelial dysfunction. In particular, recent studies have shown that preeclampsia is associated with the presence of maternal autoantibodies capable of binding to and activating the angiotensin (Ang) receptor type-1 (AT1). AT1 receptor agonistic antibodies, herein termed AT1-AA, are rarely seen in normotensive pregnant women. Since the initial discovery of these autoantibodies, considerable evidence supporting a pathophysiological role of AT1-AA in preeclampsia has accumulated.

Initial Identification of Agonistic Autoantibodies Activating the AT1 Receptor in Preeclampsia

A major advance in our understanding of preeclampsia was made by Wallukat et al, who reported that sera from preeclamptic women contain an IgG autoantibody that reacts with the AT1 receptor, a 7 transmembrane G protein coupling receptor, in a stimulatory fashion (Figure 1). They relied on a bioassay for AT1 agonistic autoantibodies (termed AT1-AA) that consists of spontaneously beating neonatal rat cardiomyocytes. They showed that AT1-AA increase the spontaneous beating rate of the cultured cardiomyocytes, a feature that is blocked by AT1 receptor antagonists but not AT2 receptor antagonists or agonists of adrenergic receptors. With affinity purification and peptide competition experiments they showed that the AT1-AA bind to a 7 amino acid sequence present on the second extracellular loop of the AT1 receptor (Figure 1). The presence of this sequence, AFHYESQ, in the cardiomyocyte contraction assay blocked antibody-induced stimulation of cardiomyocyte contraction. These remarkable findings were the first to show that preeclamptic women develop stimulatory autoantibodies against the AT1 receptor and that these autoantibodies are directed to a common epitope associated with the second extracellular loop.

Pathophysiological Role of AT1-AA in Preeclampsia

Immune mechanisms and the renin-angiotensin system are implicated in preeclampsia. These 2 concepts were united by Wallukat et al, who reported that sera from preeclamptic women contain an autoantibody that reacts with AT1 receptors in a stimulatory fashion. Subsequent to these findings, multiple other groups, including our own, showed that many features of preeclampsia could be explained by the ability of these autoantibodies to activate AT1 receptors on a variety of cells. Examples of these possibilities are reviewed below and summarized in the Table.

Role of AT1-AA on Hypercoagulation in Preeclampsia

Severe preeclampsia may be accompanied by disseminated intravascular coagulation and reduced fibrinolysis. These changes may be due to alterations in components of the coagulation and fibrinolytic systems, including tissue factor...
and plasminogen activator inhibitor (PAI)-1. These possibilities are considered below.

**Coagulation System**

Tissue factor (TF) is a 47-kDa transmembrane protein that initiates the extrinsic pathway of coagulation via formation of an enzymatic complex with factor VII/factor VIIa. Increased expression of TF is associated with placentas from women with preeclampsia. Dechend et al12 showed that AT1-AA stimulated increased TF expression in human vascular smooth muscle cells. They also showed that AT1-AA activate TF promoter/luciferase constructs after transfection into cells that contain AT1 receptors and that this activation required the presence of activating protein-I binding sites. Increased TF synthesis by vascular smooth muscle cells and the activation of the TF/luciferase reporter were blocked by losartan. IgG from normotensive pregnant women had no effect in either assay. Dechend et al12 also confirmed earlier reports showing that preeclamptic placentas exhibit increased TF expression and activity compared with placentas from normotensive pregnant women. In subsequent studies, Dorffel et al20 reported that AT1-AA stimulated monocytes to produce increased amounts of TF, a feature that could contribute to increased endothelial cell adherence. Thus, the studies of Dechend et al12 and Dorffel et al20 show that AT1-AA activates AT1 receptors, initiating a signaling cascade resulting in increased TF expression. Together these studies suggest that the action of AT1-AA on human vascular smooth muscle cells and monocytes may contribute to the hypercoagulability associated with preeclampsia.

**Fibrinolytic System**

The fibrinolytic system is best known for its role in the regulated digestion of fibrin clots.10,11 A key component of this system is plasminogen, an inactive zymogen, which is converted into the active protease plasmin by the action of plasminogen activators. Plasminogen activator activity is controlled by PAIs, of which PAI-1 is the predominant

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**Figure 1.** Schematic diagrams of AT1 receptor and the sequence of 7 amino acid antibody blocking epitope peptide. AT1-AA interacts with second extracellular loop of AT1 receptor. This interaction can be blocked by a specific 7 amino acid peptide.

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### Pathophysiological Role of AT1-AA in Preeclampsia

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physiological inhibitor of its class.\textsuperscript{21,22} PAI-1 is upregulated in placentas of preeclamptic women, leading to a reduced fibrinolytic activity.\textsuperscript{14–16} Elevated PAI-1, which occurs in the maternal circulation in preeclampsia, is believed to contribute to the hypercoagulation and fibrinolytic imbalance associated with this condition.\textsuperscript{23} Our studies originally showed that Ang II stimulates PAI-1 synthesis and secretion by human trophoblasts in a time- and concentration-dependent manner. In subsequent experiments, we found that AT\textsubscript{1}-AA, like Ang II, stimulates PAI-1 synthesis and secretion by activating AT\textsubscript{1} receptors on human trophoblasts.\textsuperscript{18} Antibody-induced PAI-1 induction was blocked by losartan and the AT\textsubscript{1} receptor epitope peptide, thereby providing strong evidence that the antibody effect is mediated through AT\textsubscript{1} receptor activation. In several other cell types, PAI-1 production is also controlled by the action of Ang II on AT\textsubscript{1} receptors. Such cells include mesangial cells,\textsuperscript{24,25} myocardial cells,\textsuperscript{26} vascular smooth muscle cells, and endothelial cells.\textsuperscript{27} We also showed that AT\textsubscript{1}-AA activates AT\textsubscript{1} receptors on human mesangial cells and induces PAI-1 secretion.\textsuperscript{18} Thus, action of maternal AT\textsubscript{1}-AA on the AT\textsubscript{1} receptors of trophoblast cells, mesangial cells, and other cell types in the maternal system is likely to contribute to the increased circulating PAI-1 and reduced fibrinolysis associated with preeclampsia.

### Role of AT\textsubscript{1}-AA on Increased Production of Reactive Oxygen Species in Preeclampsia

Reactive oxygen species (ROS) production by the placenta and maternal tissues is increased in preeclamptic women and likely contributes to the oxidative stress associated with preeclampsia.\textsuperscript{28} The identity of the ROS-producing enzymes in preeclampsia has been investigated by Dechend et al.,\textsuperscript{13} who recognized that reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase is a major source of ROS in arteriosclerosis and reperfusion injury. Several important findings emerged from their studies. First, IgG from preeclamptic women induces intracellular ROS in vascular smooth muscle cells and trophoblasts, an induction that is mediated by NADPH oxidase. Second, AT\textsubscript{1}-AA activates nuclear factor \(\kappa B\) (NF\(\kappa B\)) as a downstream target, resulting in the marked upregulation of nuclear factor \(\kappa B\). Third, ROS production is increased in preeclamptic placentas, especially in and around the blood vessels. Finally, NADPH oxidases are present in the placenta and are massively elevated in preeclampsia. They suggest that AT\textsubscript{1}-AA, through activation of NADPH oxidase, could contribute to ROS production and the inflammatory responses associated with preeclampsia.

### Role of AT\textsubscript{1}-AA in Abnormalities of Calcium Metabolism Associated With Preeclampsia

Preeclampsia is associated with abnormalities in Ca\textsuperscript{2+} metabolism and increased intracellular Ca\textsuperscript{2+} levels in platelets, erythrocytes, and lymphocytes.\textsuperscript{29,30} Haller et al.\textsuperscript{29} showed that basal intracellular free Ca\textsuperscript{2+} in platelets is substantially elevated in preeclamptic patients compared with women with uncomplicated pregnancy. This phenomenon completely disappears 6 weeks after delivery, which suggests a relevant relationship to preeclampsia. Similar studies using lymphocytes and erythrocytes showed that the intracellular free Ca\textsuperscript{2+} concentration is increased in these cells of preeclamptic patients.\textsuperscript{30,31} In addition, a more widespread dysregulation of cellular Ca\textsuperscript{2+} metabolism is also implicated in preeclampsia.\textsuperscript{29} The underlying mechanism dictating changes in intracellular free Ca\textsuperscript{2+} levels and Ca\textsuperscript{2+} metabolism in preeclampsia was investigated by Thway et al.\textsuperscript{14} from our laboratory. We found that IgG from preeclamptic patients activated AT\textsubscript{1} receptors and increased intracellular free calcium. In contrast, IgG from normotensive individuals was incapable of activating AT\textsubscript{1} receptors and calcium mobilization. The specific mobilization of intracellular Ca\textsuperscript{2+} by AT\textsubscript{1}-AA from women with preeclampsia was blocked by losartan and by the 7-amino acid epitope peptide that corresponds with a site on the second extracellular loop of the AT\textsubscript{1} receptor. Overall, our studies suggest that AT\textsubscript{1}-AA may account for increased intracellular free Ca\textsuperscript{2+} concentrations and changes in gene expression associated with preeclampsia.\textsuperscript{14}

### Role of AT\textsubscript{1}-AA on Excess sFlt-1 Secretion in Preeclampsia

Pregnancy is characterized by significant changes in the abundance of angiogenic factors, such as vascular endothelial growth factor and placental growth factor, and their antagonist, sFlt-1.\textsuperscript{32} The levels of sFlt-1 in the maternal circulation increase in the third trimester of normal pregnancy.\textsuperscript{33–35} Numerous recent reports provide convincing evidence that the level of sFlt-1 in plasma of women with preeclampsia is elevated in comparison with women with normal pregnancy.\textsuperscript{33,34,36–38} Circulating sFlt-1 binds circulating vascular endothelial growth factor and placental growth factor and prevents their interactions with their proangiogenic receptors. Administration of sFlt-1 to rats resulted in elevated blood pressure, proteinuria, and renal changes, classic features of preeclampsia.\textsuperscript{9} Thus, excessive placentald-derived sFlt-1 may contribute to endothelial dysfunction, hypertension, and proteinuria associated with preeclampsia. However, the potential mechanism for increased sFlt-1 production in preeclampsia has not been identified. We have reported recently that Ang II stimulates increased sFlt-1 by human trophoblast cells, villous placental explants, and pregnant mice.\textsuperscript{39} Subsequent to these studies, we have shown that IgG from women with preeclampsia induces the synthesis and secretion of sFlt-1 by human placental villous explants and by human trophoblast cells.\textsuperscript{40} The secreted sFlt-1 has significant antiangiogenic properties as judged by its impact on in vitro endothelial cell migration and tube formation assays. The introduction of IgG from preeclamptic patients into pregnant mice resulted in increased synthesis and secretion of sFlt-1. We also found that Ang II and AT\textsubscript{1}-AA can function additively to induce sFlt-1 secretion through AT\textsubscript{1} receptor activation.\textsuperscript{40} Overall, our findings support the view that Ang II is a key regulator of sFlt-1 synthesis and secretion during normal pregnancy\textsuperscript{39} and that the excessive accumulation of sFlt-1 observed in women with preeclampsia is because of additional activation of AT\textsubscript{1} receptors mediated by AT\textsubscript{1}-AA.\textsuperscript{41}

### Role of AT\textsubscript{1}-AA in Shallow Trophoblast Invasion in Preeclampsia

Impaired placental development resulting from shallow trophoblast invasion is a well-recognized feature of preeclampsia.
This placental abnormality results in reduced placenta perfusion, a feature that can be readily detected by Doppler sonography before 20 weeks. A recent report shows that AT₁-AA is associated with pregnant women who display impaired placental development as judged by abnormal uterine perfusion detected by Doppler sonography. Using the cardiomyocyte contraction assay, Walther et al found that the AT₁-AA was detectable between 18 and 22 weeks in women with abnormal uterine perfusion. When followed to term, these women fell into 3 groups: those who developed preeclampsia, those characterized by fetuses with intrauterine growth retardation, and those with otherwise normal outcomes. AT₁-AA was not observed in second-trimester women with normal Doppler ultrasound. Thus, AT₁-AA tracks with abnormal placental development and may serve to identify women at risk for intrauterine growth retardation and/or preeclampsia. The authors of this study suggested, as we had done earlier, that AT₁-AAs may be responsible for reduced trophoblast invasion and impaired placental development.

Placental development depends on the regulated production of proteolytic enzymes such as plasmin, a key enzyme in the fibrinolytic system. This system plays a critical role in extracellular matrix degradation to facilitate trophoblast invasion of the maternal uterus. Of particular importance in the regulation of plasmin production is the urokinase-type plasminogen activator that is synthesized by trophoblasts and is activated on association with specific receptors, urokinase-type plasminogen activator receptors, located on the surface of trophoblasts. We used an in vitro Matrigel invasion assay to show that Ang II–induced synthesis and secretion of PAI-1 in response to AT₁ receptor activation resulted in reduced trophoblast invasion. A significant stimulation of PAI-1 secretion from human trophoblasts was also observed with IgG from patients with preeclampsia. IgG obtained from normotensive pregnant patients did not stimulate PAI-1 secretion. Activation of AT₁ receptors by AT₁-AA was blocked by losartan, the 7 amino epitope peptide, and FK506, a calcineurin-specific inhibitor, suggesting that calcineurin signaling functions downstream of AT₁ receptor activation to mediate PAI-1 induction (Figure 2). Thus, activation of AT₁ receptors by AT₁-AA on human trophoblasts may contribute to increased PAI-1 production and shallow trophoblast invasion.

**Mechanism of Antibody-Induced Receptor Activation**

Multiple signaling pathways have been reported to be involved in AT₁ receptor activation mediated by AT₁-AA (Figure 2). Wallukat et al initially showed that AT₁-AA–mediated AT₁ receptor activation results in downstream activation of protein kinase C pathways in vascular smooth muscle cells. Dechend et al found that AT₁-AA increased extracellular signal–regulated kinase 1/2 phosphorylation and led to AP-1 and nuclear factor κB activation. These activated transcription factors are required for TF and NADPH oxidase induction mediated by AT₁-AA in vascular smooth muscle.
cells, trophoblast cells, and placenta.\textsuperscript{12} We have shown that the calcineurin-nuclear factor activating T-cell signaling pathway is involved in PAI-1 induction and trophoblast shallow invasion in human trophoblast cells mediated by AT\textsubscript{1}-AA.\textsuperscript{11} More recently, we revealed that calcineurin-nuclear factor activating T-cell signaling pathway is also essential for both Ang II- and AT\textsubscript{1}-AA-mediated sFlt-1 induction at the transcriptional level.\textsuperscript{39,40} In addition, Ang II and AT\textsubscript{1}-AA additively induced nuclear factor activating T-cell activity in human trophoblast cells resulting in excess sFlt-1 secretion, suggesting that additional activation of AT\textsubscript{1} receptor may be responsible for increased sFlt-1 secretion in preeclampsia.\textsuperscript{40} Thus, multiple studies imply that downstream signaling pathways involved in autoantibody-mediated AT\textsubscript{1} receptor activation are similar to those induced by Ang II.

**Physiological Basis for Autoantibody Production-Rodent Models of Preeclampsia**

The etiology of autoimmune disease remains largely unknown. Multiple factors, including genetic predisposition, maladaptive immune system, and environment challenge, have been proposed to be involved in autoantibody production.\textsuperscript{46-48} Evidence presented below suggests that the generation of AT\textsubscript{1}-AA is secondary to reduced placental perfusion and the increased maternal inflammatory response that is associated with preeclampsia.\textsuperscript{1,3,8,41,42}

**A Transgenic Model of Preeclampsia**

Takimoto et al\textsuperscript{49} created lines of transgenic mice carrying either the human renin gene or the human angiotensinogen gene. They observed that female transgenic mice carrying the human angiotensinogen gene, which displayed normal blood pressure in the nonpregnant state, developed hypertension late in gestation, but only when mated with transgenic males carrying the human renin gene. Blood pressure returned to normal after birth of the pups. The rise in maternal blood pressure correlated with an increase in secretion of human renin from the transgenic placentas late in pregnancy and an associated increase in circulating Ang II. Histopathologic examination revealed uniform enlargement of glomeruli associated with an increase in urinary protein excretion, myocardial hypertrophy, and necrosis and edema in the placenta. Dechend et al\textsuperscript{50} examined comparable lines of transgenic rats and also observed an increase in Ang II late in pregnancy and associated proteinuria, renal pathology, placental abnormalities, and hypertension that resolved with delivery. Dechend et al\textsuperscript{50} used the cardiomyocyte contraction assay to detect the presence of AT\textsubscript{1} agonistic antibody in pregnant transgenic rats at day 18 of gestation. Peptide competition experiments showed that the antibody interacted with the same 7 amino acid epitope on the second extracellular loop of the AT\textsubscript{1} receptor defined by AT\textsubscript{1}-AA obtained from women with preeclampsia. Thus, this study suggests that increased blood pressure by overproduction of Ang II in double transgenic pregnant rats may lead to decreased blood flow to placenta and is associated with the production of AT\textsubscript{1}-AA (Figure 3).

**Experimentally Induced Models of Preeclampsia in Rats**

It is a widely held view that the maternal syndrome of preeclampsia is secondary to placental abnormalities, especially those resulting from placental ischemia.\textsuperscript{43,44} In this regard, Granger and colleagues\textsuperscript{51-53} have developed a rat model of preeclampsia resulting from experimentally induced placental ischemia resulting from reduced uterine perfusion pressure (RUPP). In these rats, they observed increased maternal blood pressure, proteinuria, and other features associated with preeclampsia.\textsuperscript{52} They also investigated the placentas and maternal circulation of RUPP-manipulated rats and found tumor necrosis factor (TNF-\(\alpha\)) expression up several fold.\textsuperscript{54} More recently, they found that sera from RUPP manipulated pregnant rats enhanced endothelin synthesis by endothelial cells through AT\textsubscript{1} receptor activation.\textsuperscript{54} Linas and colleagues, in collaboration with Granger and colleagues,\textsuperscript{55,56} examined these rat models of preeclampsia for the presence of AT\textsubscript{1}-AA. They observed the presence of AT\textsubscript{1} receptor agonistic autoantibodies as judged by the cardiomyocyte contraction assay only in RUPP pregnant rats but not normal pregnant rats.\textsuperscript{55,56} TNF-\(\alpha\), an inflammatory cytokine, is induced in RUPP pregnant rats. They found that low-dose TNF-\(\alpha\) infusion in pregnant rats also resulted in increased blood pressure and the appearance of AT\textsubscript{1} receptor agonistic autoantibodies.\textsuperscript{56} Neither feature was induced by TNF-\(\alpha\) infusion into nonpregnant rats, suggesting that hypoxia and ischemia in the placenta may lead to enhanced inflammatory response and result in AT\textsubscript{1}-AA production.

![Figure 3. Molecular basis of AT\textsubscript{1}-AA production in rat models of preeclampsia: generation of AT\textsubscript{1}-AA may be secondary to placental ischemia, vascular damage, and enhanced inflammatory response. The decreased blood flow to placenta in double transgenic rats and RUPP rats leads to placental ischemia and hypoxia. This will result in endovascular damage and the enhanced inflammatory response with increased secretion of inflammatory cytokines (eg, TNF-\(\alpha\)). The resulting inflammatory cytokine secretion contributes to AT\textsubscript{1} receptor agonistic antibody production. AT\textsubscript{1}-AA will directly induce higher blood pressure and proteinuria via AT\textsubscript{1} receptor activation. This may eventually lead more hypoxia, endovascular damage, and enhanced inflammatory response. Thus, we speculate that hypoxia because of reduced placental perfusion may lead to an inflammatory response that contributes to the generation of AT\textsubscript{1}-AA. The resulting AT\textsubscript{1}-AA may further contribute to decreased trophoblast invasion, increased hypoxia, and an enhanced inflammatory response, leading to more AT\textsubscript{1}-AA production. Therefore, reduced placental perfusion, hypoxia, inflammatory response, and AT\textsubscript{1}-AA production act as a detrimental cycle to contribute to pathophysiology of preeclampsia.](http://hyper.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.116.111568)
In summary, AT1-AA is present in 3 different animal models of preeclampsia: double transgenic rats, chronic RUPP, and low-dose TNF-α infusion during pregnancy. These findings suggest that the generation of AT1-AA is a secondary event to reduction in placental perfusion leading to chronic inflammation (Figure 3). The decreased blood flow to placenta leads to placental ischemia and hypoxia. This will result in endovascular damage and the enhanced inflammatory response with increased secretion of inflammatory cytokines (eg, TNF-α). The resulting inflammatory cytokine secretion may lead to AT1 receptor–agonistic antibody production in ways that are not yet understood. The resulting AT1-AA will contribute to higher blood pressure and proteinuria via AT1 receptor activation. In addition, increased AT1-AA may also further decrease trophoblast invasion and spiral artery remodeling. This eventually leads to more hypoxia, endovascular damage, and potent inflammatory response. Thus, we speculate that hypoxia because of reduced placental perfusion may lead to an inflammatory response that contributes to the generation of AT1-AA. The resulting AT1-AA may further contribute to decreased trophoblast invasion, increased hypoxia, and an enhanced inflammatory response, leading to more AT1-AA production. Therefore, reduced placental perfusion, hypoxia, inflammatory response, and AT1-AA production act as a detrimental cycle to contribute to the pathophysiology of preeclampsia. These experimentally induced models of preeclampsia in the pregnant rat may provide a valuable model system to determine the physiological basis for autoantibody production.

**Potential Therapeutic Effects of Small Antibody Blocking Peptides**

Currently there is no effective treatment for preeclampsia, and severe cases often require premature delivery of the infant. If maternal circulating AT1-AA contributes to the pathophysiology of preeclampsia, as the multiple studies from us and others suggest, blocking the action of these autoantibodies with the 7 amino acid epitope peptide may provide significant therapeutic benefit. This expectation is supported by previous in vitro studies showing that AT1-AA typically recognizes a 7 amino acid sequence present on the second extracellular loop of the AT1 receptor (Figure 1), and the ability of AT1-AA to activate AT1 receptors on various cell types can be blocked by the 7 amino acid antibody blocking epitope peptide. Our current studies show that this peptide can neutralize AT1-AA in vivo and thereby prevent autoantibody-induced sFlt-1 production in pregnant mice. Thus, the use of epitope peptide therapy to block the action of Ang receptor–activating autoantibodies has the potential of being a safe and effective treatment of preeclampsia (Figure 1).

**Conclusion**

In 1999, Wallukat et al reported their remarkable findings that sera from women with preeclampsia contain autoantibodies that react with the AT1 receptor in a stimulatory fashion. These findings provided a new way of thinking about the abnormalities associated with preeclampsia. As described here, these important findings have been extended in numerous ways showing that these autoantibodies activate AT1 receptors on cardiac myocytes, trophoblast cells, endothelial cells, mesangial cells, and vascular smooth muscle cells, among others. Although the studies show that the AT1-AA activates AT1 receptors on a variety of cell types and provokes biological responses that are relevant to the pathophysiology of preeclampsia, the etiology or causality of the disease still remains elusive.

**Sources of Funding**

This work was supported by National Institutes of Health grants HL076558 (to Y.X.) and HD34130 (to R.E.K.).

**Disclosures**

None.

**References**


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Hypertension. 2007;50:269-275; originally published online June 18, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.091322
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

The online version of this article, along with updated information and services, is located on the
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