Attenuated Responses to Angiotensin II in Follitropin Receptor Knockout Mice, a Model of Menopause-Associated Hypertension

Danesh Javeshghani, Rhian M. Touyz, M. Ram Sairam, Agostino Virdis, Mario Fritsch Neves, Ernesto L. Schiffrin

Abstract—Activation of the renin-angiotensin system has been implicated in the development of hypertension in menopausal women. We investigated whether blood pressure is elevated and whether angiotensin II (Ang II)-induced vascular reactivity is increased in follitropin receptor knockout (FORKO) female mice. These mice are estrogen-deficient and have characteristics similar to postmenopausal women. Serum estradiol levels were significantly reduced in FORKO versus wild-type mice (1.4±0.2 versus 15±3 pg/mL, P<0.01). Blood pressure, measured by telemetry, was significantly increased in FORKO (120±2/92±2 mm Hg) compared with wild-type counterparts (110±1/85±2 mm Hg, P<0.05). Vascular dose responses to acetylcholine (endothelium-dependent dilation) and sodium nitroprusside (endothelium-independent dilation) were not different. Ang II–induced vasoconstriction was blunted in FORKO compared with wild-type mice (P<0.05). Media-to-lumen ratio was significantly increased in FORKO (6.2±0.5%) versus control mice (5.2±0.3%), indicating vascular remodeling. Mitochondrial superoxide levels, assessed by immunoblotting, was reduced by 40% in FORKO compared with wild-type mice (P<0.01). This was associated with decreased circulating Ang II levels in FORKO versus control mice. These data indicate that FORKO mice have increased blood pressure, vascular remodeling, and attenuated vascular responses to Ang II. Our findings suggest that vascular Ang II signaling is downregulated in female FORKO mice and that Ang II may not play an important role in blood pressure elevation in this model of menopause-associated hypertension. (Hypertension. 2003;42[part 2]:761-767.)

Key Words: renin-angiotensin system ■ estrogen ■ hypertension, experimental ■ resistance

Cardiovascular disease, of which hypertension is a major risk factor, is a leading cause of death in developed countries. Whereas premenopausal women have reduced risk compared with men, the incidence of cardiovascular disease increases significantly after menopause.1 Because ovarian activity decreases in the postmenopausal period, it is believed that reduced estrogen levels contribute to development of hypertension and to the increase in cardiovascular disease in postmenopausal women. Hormone replacement therapy (HRT) has been used to treat postmenopausal symptoms and to reduce the risk of cardiovascular disease.2 However, recent large clinical trials failed to demonstrate cardiovascular beneficial effects of HRT and have even suggested increased cardiovascular risk during the initial treatment period.3 Estrogen has rapid (nongenomic) and long-term (genomic) actions on many target tissues. These effects are mediated through at least two estrogen receptors called ERα and ERβ that may exist as nuclear or membrane-bound receptors.4 The resulting estrogen-estrogen receptor complexes serve as transcription factors that alter gene expression.4 In the cardiovascular system, estrogen receptors are expressed in endothelial, smooth muscle, and myocardial cells.5 The effects of estrogen on vascular tone and inhibition of vascular smooth muscle cell growth have been attributed in part to modulation of the renin-angiotensin system. In vascular smooth muscle cells, estrogen causes downregulation of angiotensin type 1 receptor (AT1R) and decreases angiotensin (Ang II)-mediated signaling.6 In vitro studies of vascular injury indicate that estradiol prevents vascular remodeling and protects against endothelial damage.7 In the heart, estradiol inhibits proliferation of cardiac fibroblasts and deposition of extracellular matrix.8 Thus estrogen appears to have a protective effect in processes associated with cardiovascular injury. Numerous studies have demonstrated that blood pressure increases in ovariectomized rats and that estrogen reverses these effects.9,10

Ovariectomy is a drastic surgical measure that involves extirpation of the entire gland and its connection to eliminate the major sources of estrogen and progesterone. This procedure, however, may not closely resemble the postmenopausal

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From the Experimental Hypertension (D.J., R.M.T., A.V., M.F.N., E.L.S.) and Molecular Reproduction Research Laboratories (D.J., M.R.S.), Clinical Research Institute of Montreal, Montreal, Ontario, Canada.
Correspondence to Rhian M. Touyz, MD, PhD, Clinical Research Institute of Montreal, Quebec, 110 Pine Ave West, Montreal, H2W 1R7, Canada.
E-mail touyzr@ircm.qc.ca
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phase in women. We recently characterized a mouse model in the SV129 genetic background in which follicle-stimulating hormone (FSH) receptor gene is ablated, creating a follicle-stimulating hormone receptor knockout (FORKO) mouse that exhibits changes that occur in postmenopausal women. FORKO mice have ovarian insufficiency, low estrogen levels with functionally responsive estrogen receptors, and increased testosterone levels.\textsuperscript{11–13} They have osteoporosis, are hypercholesterolemic, and gain weight. However, because nothing is known about the cardiovascular status in these mice and it is unclear whether hypertension develops in FORKO mice, we assessed blood pressure and vascular structure and function in this aberrant hormonal environment. Furthermore, since estrogen has been implicated to negatively influence Ang II actions, we questioned whether Ang II-mediated actions are upregulated in estrogen-deficient mice.

**Methods**

**Animals and Blood Pressure Measurement**
The study was approved by the Animal Ethics Committee of the Clinical Research Institute of Montreal and carried out according to the recommendations of the Canadian Council for Animal Care. FORKO mice, which we have characterized,\textsuperscript{11,12} and wild-type control mice (14 to 16 weeks; 6 to 9 per group per experiment) were studied. Animals were implanted with blood pressure transmitters according to published methods.\textsuperscript{11,12} Isoflurane was used for anesthesia. After 1 week of recovery, data were collected for 10 seconds every 5 minutes for 7 days. Daily morning blood pressure readings were pooled and used for analysis.

**Plasma Levels of Estradiol and Testosterone**
Levels of circulating estradiol and free testosterone were measured in FORKO and wild-type mice by radioimmunoassay according to published methods.\textsuperscript{11,12}

**Preparation of Small Mesenteric Arteries**
Animals were anesthetized (0.03 mL/30 g body wt, equal volume of ketamine hydrochloride [100 mg/mL] and xylazine [20 mg/mL] IP). A second-order branch of the mesenteric arterial tree, representative of resistance arteries, was dissected and mounted as a pressurized system, as detailed elsewhere.\textsuperscript{15} Media thickness and lumen diameter were measured with the use of a microcomputer-based video imaging system. Media cross-sectional area (CSA) was calculated as previously described.\textsuperscript{15} Ang II–induced vascular constriction, endothelium-dependent relaxation (acetylcholine-mediated) and endothelium-independent relaxation (sodium nitroprusside [SNP]-mediated) were determined according to previously described methods.\textsuperscript{15}

**Measurement of TBARS**
Thiobarbituric acid–reacting substances (TBARS) were determined as an index of oxidative stress by assaying malonaldehyde–bis (MDA).\textsuperscript{16} Cardiac blood was collected into tubes containing EDTA (tubes = 7/group). Samples were microcentrifuged for 1 minute, and plasma was collected and stored at −80°C until use. Plasma was mixed with 2% BHT (wt/vol) and Quantita reagent (0.375% [wt/vol] thiobarbiturate-reacting substances [TBA], 60% [vol/vol] 0.25N HCl, 3% [wt/vol] trichloroacetic acid). The mixture was vortexed, boiled at 95°C, and centrifuged at 50°C for 10 minutes. Absorption by the supernatant was measured spectrophotometrically at 535 nm. Values were determined according to previously described methods.\textsuperscript{15}

**Preparation of Vascular Tissue for Western Blot**
Extracts of cleaned mesenteric arteries were prepared in lysis buffer (final concentrations in PBS, 1% nonidet P40; 0.5% sodium deoxycholate; 0.1% SDS; 1 mM PMSF, 1 μg/mL leupeptin; 1 μg/mL aprotonin; 1 μg/mL pepstatin; 1 mM NAL (NaVO₃)). Electrophoresis at 75 to 150 V and transfer at 100 V to PVDF membrane was performed. Expression of vascular AT₁R, ERα, and ERβ was assessed with the use of specific antibodies (anti-AT₁R [1:500], Alpha Diagnostic), rat anti-ERα, and rabbit anti-ERβ (1:1000), as described previously.\textsuperscript{11,12} The secondary antibody concentration was 1:1000. Immunoreactive proteins were detected by chemiluminescence. Blots were analyzed densitometrically (Image-Quant Software, Molecular Dynamics).

**Measurement of Vascular Superoxide (·O₂⁻) and NAD(P)H Oxidase Activity**
The aorta was removed and placed in ice-cold PBS, cleaned from adherent tissues, and used as previously described.\textsuperscript{17} Generation of superoxide was measured in basal conditions and in the presence of NADH (100 μm) in the absence and presence of superoxide dismutase (SOD, 8.5 U/mL) and tempol (SOD mimetic) (5 mmol/L). Chemiluminescence was expressed as relative light units/min per milligram.

**Collagen Staining**
Mice were perfused with PSS,\textsuperscript{13} then with Bovine’s fixative. Cardiac tissue was collected, washed in 70% ethanol, and then paraffin-embedded. Sections were cut and stained for collagen with 0.1% sirius red. Collagen deposition was evaluated in 8 fields per section with the use of an image analysis system (Northern Eclipse 5.0, EMPIX Imaging Inc). The perivascular collagen area was normalized to vessel luminal area. Four sections were studied per rat (n = 6/group).

**Angiotensin II Radioimmunoassay**
Circulating Ang II levels were measured as previously described.\textsuperscript{18} Under anesthesia, blood was collected in EDTA-containing tubes (n = 9 per group). With extraction buffer, samples were cleared at 170g, 30 minutes, 4°C. Each of the 3 eluted samples\textsuperscript{18} were pooled, lyophilized, reconstituted, and quantified by RIA with the use of 125I–labeled human Ang II and a rabbit antibody (provided by Dr T.L. Reudelhuber), which reacts with Ang II, Ang III, and Ang IV but not with Ang I. Radioactivity was measured with a gamma counter. Values are expressed as picogram per milliliter of plasma.

**Statistical Analysis**
Dose-response curves were compared by ANOVA for repeated measures. The Student t test was used for comparison of two means where appropriate. A value of P < 0.05 was considered significant.

**Results**

**Biochemical Parameters, Blood Pressure, and Heart Rate**
As shown in the Table, plasma estrogen levels were very low (P < 0.01), whereas plasma testosterone was significantly increased (P < 0.01) in FORKO mice compared with age-matched wild-type control mice. Systolic blood pressure, diastolic blood pressure, and mean arterial pressure, measured by radiotelemetry, were significantly higher in the FORKO group compared with control mice (P < 0.05) (Figure 1). Heart rate was significantly lower in the FORKO mice.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild-Type Mice</th>
<th>FORKO Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol, pg/mL</td>
<td>14.6 ± 2.4</td>
<td>1.4 ± 0.2*</td>
</tr>
<tr>
<td>Testosterone, ng/mL</td>
<td>6.8 ± 0.7</td>
<td>32.3 ± 4.3*</td>
</tr>
</tbody>
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*P < 0.01 vs wild-type counterpart.
Morphology of Mesenteric Resistance Arteries in FORKO
Media-to-lumen ratio of resistance arteries was significantly greater in FORKO mice (6.2%±0.5%) compared with control mice (5.2%±0.3%), demonstrating vascular remodeling. CSA was 9.76×10^3±0.79×10^3 \mu m^2 in wild-type versus 11.04×10^3±0.67×10^3 \mu m^2 in FORKO mice. Although CSA tended to be higher in FORKO female mice than in their wild-type counterparts, the differences were not significant, suggesting eutrophic remodeling.

Endothelial Function of Mesenteric Resistance Arteries in FORKO
Vasodilatory responses to acetylcholine were not different between FORKO and wild-type groups (Figure 2a). Endothelium-independent vasodilatory responses to maximal doses of SNP were not different between groups (Figure 2b).

Responses to Angiotensin II
The vasoconstrictor response to Ang II was significantly lower in FORKO compared with control mice (Figure 3). Vasoconstrictor responses started to diverge at 10^(-5) mol/L and became significantly different at 10^(-4) mol/L. These data demonstrate blunted Ang II–induced vasoconstriction in FORKO mice.

Vascular ·O_2^- and NAD(P)H Oxidase Activity
To evaluate whether generation of vascular reactive oxygen species (ROS) is altered in estrogen-deficient mice, basal and NADH-stimulated production of superoxide (·O_2^-) was measured in aortic rings (Figure 4). Basal ·O_2^- levels were not different between wild-type and FORKO groups (5.9±0.39×10^3 versus 4.8±0.57×10^3 RLU/min/mg dry tissue wt). Addition of NADH increased lucigenin chemiluminescence in both groups. The increase was not significantly different between FORKO (165±18×10^3 RLU/min per milligram) and wild-type mice (269±56×10^3 RLU/min per milligram) (Figure 4). Addition of SOD and tempol reduced lucigenin chemiluminescence in both groups. We also determined TBARS in plasma, as a measurement of systemic oxidative stress assayed by malondialdehyde. The level of TBARS was not significantly different between FORKO (4.09±0.21 \mu mol/L) and control mice (3.69±0.18 \mu mol/L).

Western Blot Analysis of AT_1 and Estrogen Receptors
To evaluate whether downregulation of AT_1R in FORKO may be due to increased circulating Ang II levels, we measured plasma Ang II by RIA. The level of Ang II was not achieved (Figure 5). This was associated with increased content of ERβ in FORKO mice (P<0.05). The average density for ERα was lower in FORKO than in control mice, but statistical significance was not achieved (P=0.057) (Figure 5).

Plasma Angiotensin II
To evaluate whether downregulation of AT_1R in FORKO mice may be due to increased circulating Ang II levels, we measured plasma Ang II by RIA. The level of Ang II was significantly lower in FORKO compared with control mice (1.11±0.72 versus 5.32±1.87 pg/mL, P<0.05).

Figure 1. Bar graphs show blood pressure in wild-type and FORKO mice measured by radiotelemetry. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and MAP, mean arterial pressure. *P<0.05 vs wild-type group.

Figure 2. Line graphs show endothelium-dependent (a) and endothelium-independent relaxation (b) of mesenteric resistance arteries from wild-type and FORKO mice. Each data point is mean±SEM of 8 rats.

Figure 3. Line graphs show Ang II–induced contractile responses in arterial segments from wild-type and FORKO mice. Each data point is mean±SEM of 8 rats. *P<0.05 vs wild-type counterpart.

Figure 4. Bar graphs show basal ·O_2^- and NADH-induced generation of ·O_2^- in aortic segments from wild-type and FORKO mice as measured by lucigenin chemiluminescence. In some experiments, SOD or tempol (SOD mimetic) were added. SOD and tempol abolished the lucigenin signal indicating that chemiluminescence derived from ·O_2^- . RLU indicates relative light units.
Extracellular Matrix Deposition
As an index of altered extracellular matrix composition in hypertension, we evaluated cardiac collagen content, which has previously been found to be increased in hypertensive models.\(^{19}\) We found that perivascular collagen content was significantly greater in FORKO mice compared with wild-type mice, as demonstrated in Figure 6. The density of perivascular collagen to lumen ratio was 0.28±0.03 in wild-type and 0.41±0.03 in FORKO mice (\(P<0.05\)).

Discussion
Major findings from the present study demonstrate that in estrogen-deficient FORKO mice (1) blood pressure is increased, (2) resistance arteries undergo structural remodeling, and (3) Ang II–induced vascular contraction is blunted. These changes are associated with reduced circulating Ang II levels, decreased abundance of vascular \(\text{AT}_1\) receptors, and increased expression of vascular \(\text{ER}\beta\). There was no evidence of impaired endothelium-dependent relaxation as assessed by acetylcholine-induced responses, and oxidative stress was not increased in FORKO mice.

The role of estrogen in the pathogenesis of hypertension, particularly in the postmenopausal period, has recently been questioned. Many studies in rats have demonstrated that blood pressure is increased in ovariectomized rats,\(^{8,10,20}\) a change that is reversed by estradiol treatment. Similarly, estrogen-treated male hypertensive rats have lower blood pressure than untreated counterparts.\(^{21,22}\) However, there is increasing experimental and clinical evidence disputing the beneficial effect of estrogen in hypertension and cardiovascular disease.\(^3\) In estrogen receptor (\(\alpha,\beta\)) double-knockout mice that lack both nuclear receptors, blood pressure, measured by the tail-cuff method, was found to be similar to that in wild-type counterparts.\(^{23}\) Treatment with 17\(\beta\) estradiol did not influence blood pressure in either wild-type or double-knockout mice.\(^{23}\) Similarly, in mice treated with estrogen pellets for 60 days, blood pressure was not altered.\(^{24}\) The impact of genetic background in influencing these parameters is an important consideration in resolving these apparent paradoxical situations. Few experimental studies have focused specifically on the relation between estrogen and development of hypertension in menopause. To address this, in an experimental setting, we examined FORKO mice, which exhibit a reduced production of estrogen as a result of the gene inactivation of FSH receptors. We previously demonstrated that these mice are estrogen-deficient and have functionally active estrogen receptors, increased testosterone levels, osteoporosis, and weight gain.\(^{11–13}\) In the present study, we show that systolic and diastolic blood pressure, as
measured by radiotelemetry, a maneuver that eliminates operator-induced stress during handling, are significantly elevated in FORKO mice. These findings support FORKO mice as a model for menopause, which typically is associated with development of hypertension.

Small arteries typically undergo structural changes (vascular remodeling) in hypertension. Cellular processes associated with this include alterations in vascular smooth muscle cell growth, cell migration, rearrangement of vascular components, and increased abundance of extracellular matrix proteins.\(^{25}\) In FORKO mice, vascular media was thickened in resistance arteries and media-to-lumen ratio was significantly increased compared with wild-type control mice. Furthermore, in the heart, perivascular collagen deposition was increased, suggesting increased vascular fibrosis. The cross-sectional area was not different in vessels from FORKO and control groups, indicating that small arteries undergo eutrophic (no change in media mass) rather than hypertrophic remodeling (increased media mass). The manifestation of these structural changes as early as 4 months in FORKO female mice is significant; pending further examination, it is interesting to speculate that further chronic deficiency and aging may aggravate these conditions. The mechanisms contributing to vascular remodeling and development of hypertension in FORKO mice are unclear. We first questioned whether Ang II could play a role. This is based on the fact that Ang II is a potent mitogenic vasoactive peptide\(^{26,27}\) and that it contributes to vascular remodeling in experimental models of hypertension and in patients with essential hypertension.\(^{27}\) In addition, Ang II has been implicated in hypertension associated with estrogen deficiency.\(^{6,27–29}\) Furthermore,\(^{27–29}\) estrogen attenuates Ang II–mediated actions.\(^{6,30}\)

To investigate whether Ang II effects are upregulated in FORKO mice, we assessed contractile responses of small mesenteric arteries to increasing concentrations of Ang II. Contrary to our expectations, Ang II–mediated contraction was markedly blunted in arteries from FORKO mice. This was associated with significant downregulation of vascular AT\(_1\) receptor content and decreased circulating levels of Ang II. Mechanisms underlying reduced circulating Ang II levels are unclear but may be secondary to decreased renin release associated with increased blood pressure. However, these aspects await clarification in this model. Taken together, these data suggest that in our estrogen-deficient FORKO mice, activation of the vascular Ang II system is attenuated. These findings are in contrast to other studies, which reported that estrogen deficiency results in overexpression of AT\(_1\) receptors\(^{8}\) and that in estrogen-treated rats, Ang II–induced vasoconstriction is reduced.\(^{31,32}\) Processes contributing to decreased AT\(_1\) receptor abundance in FORKO female mice are unclear. Previous studies demonstrated that nitric oxide (NO) causes downregulation of AT\(_1\) receptor gene transcription in cultured cells.\(^{33}\) Furthermore, NO production by endothelial nitric oxide synthase is mediated by nongenomic actions of ER\(\alpha\).\(^{34}\) Since ER\(\alpha\) expression was increased in vessels from FORKO mice, it could be possible that NO bioavailability is increased, which may in turn influence AT\(_1\) receptor expression. However, this awaits clarification.

We also investigated the possibility that increased oxidative stress may play a pathophysiological role in the development of hypertension in FORKO mice. Extensive evidence indicates that production of reactive oxygen species by NAD(P)H oxidase is increased in hypertension.\(^{35,36}\) However, in FORKO mice, vascular levels of superoxide and NAD(P)H oxidase were not altered, suggesting that oxidative stress is not increased in our model. This was further supported by the findings that indicate there were no significant change in plasma TBARS, a marker of global oxidative stress.

Despite vascular remodeling and altered vascular reactivity to Ang II in FORKO mice, neither endothelium-dependent nor endothelium-independent vasodilatation were altered. This was evidenced by similar responses to acetylcholine and sodium nitroprusside in FORKO and control groups. Our findings of normal endothelial function to acetylcholine in estrogen-deficient mice is consistent with other data. Rubanyi et al\(^{17}\) demonstrated that acetylcholine-induced relaxation in aorta of ER\(\alpha\) knockout (ERKO) and wild-type mice were similar, despite reduced basal NO in ERKO. Riveiro et al\(^{38}\) measured percent relaxation in response to acetylcholine and demonstrated no difference in the vascular response of ovariectomized and sham-ovariectomized hypertensive rats. Together with our data from this study, these findings suggest that estrogen deficiency may not necessarily be associated with impaired endothelium-dependent relaxation.

Decreased circulating estrogen in FORKO may be compensated for by upregulation of its receptor(s) or increased receptor affinity toward its ligand. In fact, our results show that abundance of ER\(\alpha\) was increased, with ER\(\beta\) showing a tendency to decrease in small arteries from FORKO compared with wild-type mice. ER\(\alpha\) and ER\(\beta\) mediate estrogenic effects through genomic and nongenomic mechanisms. The functional significance of these receptors in the vasculature remains unclear. It has been suggested that ER\(\alpha\) induces vasoconstriction, whereas ER\(\beta\) mediates vasodilation. This was demonstrated in studies from estrogen-treated ER\(\beta\) knockout mice. In endothelium-denuded aorta from ER\(\beta\) knockout mice, estrogen induced significant vasoconstriction. These mice have hypertension with aging and exhibit loss of outward K\(^+\) currents in vascular smooth muscle cells.\(^{39}\) In our model, increased content of ER\(\alpha\) and relatively decreased ER\(\beta\) may contribute, at least in part, to vascular changes associated with development of hypertension. However, we cannot exclude the possibility that other factors independent of estrogen may play a role. A possible candidate is testosterone, which is increased in FORKO female mice. This is supported by findings from Reckelhoff and colleagues,\(^{40,41}\) who demonstrated that aged SHR, which have features of postmenopausal hypertension, have significantly elevated plasma testosterone levels. In that model, menopausal-associated hypertension was also associated with enhanced activation of the renin-angiotensin system and increased oxidative stress.\(^{40}\) Clinical studies have also identified a positive relation between free testosterone and hypertension in postmenopausal women.\(^{42}\) The pathophysiological role of testosterone in the development of hypertension in FORKO is unclear and is currently under investigation.
In conclusion, we have identified a novel model of menopause-associated hypertension. Increased blood pressure in estrogen-deficient FORKO mice is associated with eutrophic vascular remodeling, blunted Ang II reactivity, and normal endothelial function. Mechanisms underlying these phenomena do not appear to be Ang II–dependent, and oxidative stress does not seem to play a major role. Based on our current data, it is reasonable to postulate that peripheral conversion of testosterone to estrogen does not occur in our animals, as many estrogen sensitive targets are affected. Our findings provide novel data suggesting that hypertension associated with estrogen deficiency in FORKO mice is not mediated through activation of the renin-angiotensin system.

**Perspectives**

Estrogen deficiency has been implicated to play an important role in menopause-associated hypertension. These effects have been attributed to activation of the renin-angiotensin system and increased oxidative stress. However, results from recent clinical trials failed to demonstrate beneficial cardiovascular effects of HRT in postmenopausal women. These data, together with experimental studies that did not show an inverse relation between estrogen levels and blood pressure, raise the question of the exact role of sex hormones in the pathogenesis of hypertension in menopause. In the present study, we demonstrate that blood pressure is increased and small arteries underlie vascular remodeling in female FORKO mice, a model of menopause. These processes, which are associated with estrogen deficiency and testosterone excess, appear to be Ang II–dependent and do not seem to involve redox-sensitive pathways. Thus, we have identified a novel model of menopause-associated hypertension. Further characterization of the cardiovascular system in these mice may allow for a clearer understanding of the pathophysiological processes underlying hypertension in menopause.

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