Estradiol Induces Discordant Angiotensin and Blood Pressure Responses to Orthostasis in Healthy Postmenopausal Women

Paula J. Harvey, Beverley L. Morris, Judith A. Miller, John S. Floras

Abstract—Postmenopausal estrogen replacement therapy (ERT) is reported to increase angiotensin II under resting conditions. To determine the implications of this increase for cardiovascular regulation during simulated orthostasis, blood pressure (BP), heart rate (HR), renin, angiotensinogen, angiotensin II, and aldosterone were measured at rest and during lower body negative pressure (LBNP; −10, −20, and −40 mm Hg). We studied 13 normotensive postmenopausal women (54±2 [mean±SE] years) before and after 1 month of oral estradiol 2 mg daily, and 14 premenopausal women. LBNP activated the renin-angiotensin system acutely in premenopausal but not postmenopausal women. Resting renin and aldosterone were unaffected by estradiol, whereas angiotensinogen (P<0.001) and angiotensin II (P<0.01) increased. Renin, aldosterone, and HR responses to LBNP (which tended to be less in postmenopausal women [P=0.06]) were not affected by estradiol. Importantly, angiotensin II was higher on estradiol during all stages of LBNP, and increased 70% above resting values at the end of this stimulus (P<0.05), yet BP was significantly lower, both at rest (P<0.05) and during LBNP (P<0.01). In summary, in normotensive postmenopausal women, estradiol increases angiotensin II, but not aldosterone, at rest and during orthostatic stress, yet lowers, rather than raises, BP under both conditions. Downregulation of vascular and adrenal responsiveness to angiotensin II may protect healthy women against this activation. Loss of such protection may elevate BP and have adverse implications for women with conditions that impair their capacity to counteract the pathological actions of angiotensin II. This may contribute to higher cardiovascular event rates reported in recent ERT trials. (Hypertension. 2005;45:399-405.)

Key Words: estrogen • blood pressure • angiotensin II • renin-angiotensin system

Estradiol influences the human renin-angiotensin system (RAS) through several pathways. The promoter region in the angiotensinogen gene is responsive to estrogen.1 Administration of exogenous estrogen to premenopausal women in contraceptive formulations2 and to postmenopausal women as estrogen replacement therapy (ERT)3 increases plasma concentrations of this renin substrate. Furthermore, estrogen administration for these purposes has been shown to increase plasma angiotensin II,2,4,5 with either no change;6,7 or a decrease in plasma renin5,7 and a concurrent decrease in angiotensin-converting enzyme (ACE) activity.5,8 Conversely, estrogen deficiency has been associated with augmentation of ACE synthesis and activity9 and upregulation of the angiotensin II type 1 (AT1) receptor,10 the primary mediator of the hemodynamic, endocrine, and mitogenic actions of angiotensin II.

Increased generation of angiotensin II with estrogen is thought to exert a negative feedback that ultimately results in overall suppression of the RAS through inhibition of renin secretion.11 This hypothesis would explain the very modest blood pressure (BP) elevation noted with premenopausal contraceptive estrogen administration2 and its absence and even BP reduction noted in some postmenopausal women receiving ERT.3,7,12,13 However, a recent study by Chidambaram et al, which examined the RAS at different phases of the menstrual cycle, showed increased renin, plasma renin activity, and aldosterone during the high estrogen–progestin luteal phase (days 15 to 24) when compared with the low estrogen–progestin early follicular phase (days 3 to 6) of the menstrual cycle.14 Furthermore, the luteal phase was associated with an augmented renin, angiotensin II, and aldosterone response to simulated orthostatic stress. Importantly, despite this evidence of net chronic and augmented acute activation of the RAS, when compared with the low-estrogen phase of the cycle, the luteal phase was associated with lower resting BP and diminished orthostatic tolerance.14

This apparent discordance between the effects of high endogenous and exogenous estrogen on elements of the RAS and on BP regulation requires further investigation. Previous human studies of this interaction in response to exogenous estrogen administration have measured individual components of the RAS, including angiotensin II, only in the resting supine or seated positions.2–5,13 Such data provide little...
insight into the potential contribution of estrogen and the RAS to the dynamics of cardiovascular regulation in ambulatory postmenopausal women. The latter information is fundamental to any meaningful interpretation of adverse cardiovascular event rates reported in recent clinical trials. In the present study, we therefore determined, in addition, the acute RAS and systemic hemodynamic responses to graded lower body negative pressure (LBNP) to simulate levels of orthostatic stress. Healthy normotensive postmenopausal women were studied before and after treatment with chronic oral 17β-estradiol. We tested the hypothesis that any estrogen-induced activation of the RAS would result in higher BP before and during LBNP. Healthy normotensive premenopausal women were studied under identical experimental conditions to characterize the normal reference response to this stimulus.

**Methods**

Thirteen postmenopausal and 14 premenopausal women were recruited from our ambulatory care clinics and by advertisement. All subjects were deemed healthy as determined by medical history, physical examination, and hematologic and biochemical screening. All were normotensive (BP ≤140/90 mm Hg), nonobese, non-smokers, and were using no medications. Assessment of 24-hour urinary sodium excretion was performed to assess average dietary sodium intake and to exclude any subjects with markedly salt-deficient or salt-excessive diets. Postmenopausal women required either a history of at least 12 months of amenorrhea if the uterus was intact or a previous hysterectomy, combined with biochemical evidence of menopause (serum follicle-stimulating hormone [FSH] concentration ≥20 IU/L), and abstinence from hormone replacement therapy for ≥2 months before study entry. Premenopausal subjects had a regular menstrual cycle averaging 25 to 35 days and were not receiving any oral contraceptive formulation. Pregnancy was excluded by a negative β-human chorionic gonadotropin test. Our Human Subjects’ Review Committees approved this protocol, and all subjects provided signed written consent.

**Protocol**

Premenopausal subjects were studied during the mid-late follicular phase (estrogen relatively unopposed by progestin) defined as days 5 to 13 of the menstrual cycle. Subjects abstained from alcohol and caffeine for 24 hours before the study.

Studies began at ~8:30 AM. Subjects lay supine in LBNP chamber connected to a vacuum source controlled by a rheostat. An 18-gauge catheter was inserted into the right antecubital vein for blood sampling. Heart rate (HR) was determined continuously from lead II of an ECG. Arterial BP was measured from the left arm at 1-minute intervals by an automatic cuff recorder (Dinamap Pro 100; Critikon LLC).

Subjects lay quietly for 10 minutes to establish baseline values. Blood was then sampled for measurement of serum 17α-hydroxyprogesterone acetate 10 mg tablets once daily for 12 days to convert the endometrium from the follicular to the secretory state.

**Analytical Methods**

Serum concentrations of FSH and 17β-estradiol were analyzed using a commercially available radioimmunoassay kit (Boehringer). Urine sodium concentration was measured by flame photometry.

Blood for the measurement of the RAS components was collected into prechilled tubes that contained ethylenediaminetetraacetate and, for the angiotensin II samples, an angiotensinase inhibitor (0.1 mL Bestatin Solution; Buhlmann Laboratories AG, Switzerland). After centrifugation, plasma samples were stored at ~70°C until analysis. Angiotensinogen was measured indirectly by converting endogenous angiotensinogen to angiotensin I and then quantitating the amount of angiotensin I by radioimmunoassay. Conversion was performed by incubating the plasma with an excess amount of exogenous renin at 37°C for 18 hours (Calbiochem, San Diego, Calif). After measuring the produced angiotensin I, the endogenous angiotensin I obtained before incubation was subtracted.

Active plasma renin was measured by a 2-site immunoradiometric assay in which 2 monoclonal antibodies to human active renin are used. One antibody was coupled to biotin, whereas the second was radiolabeled for detection. The sample that contained active renin was incubated simultaneously with both antibodies to form a complex. The radioactivity of this complex was directly proportional to the amount of immunoreactive renin that was present in the sample.

Plasma renin activity was determined by the quantitation by radioimmunoassay (New England Nuclear kit) of angiotensin I generated after incubation of plasma at 37°C for 1.5 hours. With this method, the amount of angiotensin I generated in vitro in plasma specimens under controlled conditions is assumed as an index of renin activity in vivo.

Angiotensin II was measured by a competitive radioimmunoassay kit supplied by Buhlmann Laboratories AG after plasma samples were extracted on phenylsilysilica columns. Aldosterone was measured by radioimmunoassay using the Coat-A-Count system (Diagnostic Products Corporation; Los Angeles, Calif).

**Statistical Analysis**

Continuous variables were expressed as mean±standard error of the mean, numbers or percentages. The Student *t* test was used for unpaired (premenopausal and postmenopausal) and paired (postmenopausal pre-estrogen and post-estrogen) observations. For premenopausal subjects, the average values at each level of LBNP were compared using repeated measures ANOVA. For postmenopausal subjects, the average values at each phase of the study were compared by 2-factor repeated measures ANOVA (SigmaStat for Windows Version 2.03, SPSS Inc, Jandel Scientific Corporation) with estradiol and LBNP as within-subject factors. The Student-Newman-Keuls method was used for pair-wise, post-hoc, multiple comparisons. All statistical tests were 2-tailed, with a *P*<0.05 considered the threshold for significance.

**Results**

**Baseline Characteristics**

The mean age of postmenopausal subjects was 54±2 years. Their mean body mass index was 28.6±1.5 kg/m², which reflects the overweight nature of this population and is identical to the mean body mass index of healthy postmenopausal subjects who participated in the recent Women’s Health Initiative. Premenopausal subjects were aged 28±2 years, with a mean body mass index of 22±1 kg/m².

Subject baseline biochemical characteristics obtained at supine rest appear in Table 1. In postmenopausal subjects, plasma estradiol was significantly increased (*P*<0.001) and FSH significantly decreased (*P*<0.001) by ERT. Mean 24-hour urinary sodium excretion at entry averaged 125±9 and
TABLE 1. Baseline Hemodynamic and Biochemical Characteristics of Premenopausal and Postmenopausal Women Before and After Estradiol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premenopausal, N=14</th>
<th>Postmenopausal, N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>103±1</td>
<td>118±4†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>64±2</td>
<td>68±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>77±1</td>
<td>85±3†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>59±2</td>
<td>58±3</td>
</tr>
<tr>
<td>Estradiol, pmol/L</td>
<td>187±28</td>
<td>22±3†</td>
</tr>
<tr>
<td>FSH, IU/L</td>
<td>5.01±0.2</td>
<td>73±8§</td>
</tr>
<tr>
<td>PRA, ng ANG I/mL</td>
<td>1.03±0.27</td>
<td>1.05±0.38</td>
</tr>
<tr>
<td>Renin, µU/mL</td>
<td>18.2±3.8</td>
<td>12.8±2.3</td>
</tr>
<tr>
<td>Angiotensinogen, ng ANG I/mL</td>
<td>1804±40</td>
<td>1562±250</td>
</tr>
<tr>
<td>Aldosterone, pg/mL</td>
<td>7.4±1</td>
<td>7.5±0.5</td>
</tr>
<tr>
<td></td>
<td>32.8±6.0</td>
<td>28.5±3.9</td>
</tr>
</tbody>
</table>

Values are means±SE.

DBP indicates diastolic blood pressure; FSH, follicle-stimulating hormone; HR, heart rate; MAP, mean arterial pressure; PRA, plasma renin activity; SBP, systolic blood pressure.

*P<0.05.
†P<0.01.
‡P<0.001 vs premenopausal subjects.
§P<0.05.
¶P<0.001 after estradiol vs baseline values.

Baseline RAS and Hemodynamics

Although baseline supine mean arterial pressure (MAP) was higher in the postmenopausal women (P<0.01), both groups were clearly normotensive. Baseline HR was similar in the 2 groups. There were no significant differences between premenopausal and postmenopausal subjects in any of the components of the RAS when measured supine at baseline.

Compared with pre-estradiol values, baseline systolic blood pressure, diastolic blood pressure (DBP), and MAP were significantly lower (P<0.05) on the estradiol study day. HR was unchanged. Plasma angiotensinogen (P<0.001) and angiotensin II (P<0.01) were significantly increased by estradiol, but plasma renin and aldosterone were unchanged.

TABLE 2. Hemodynamic Responses to Lower Body Negative Pressure in Premenopausal Subjects and Postmenopausal Subjects Before and After Estradiol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>−10 mm Hg</th>
<th>−20 mm Hg</th>
<th>−40 mm Hg</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>Pre-MP</td>
<td>103±1</td>
<td>104±1</td>
<td>100±2*</td>
<td>96±2†</td>
</tr>
<tr>
<td></td>
<td>PMP before estradiol</td>
<td>118±4</td>
<td>115±3</td>
<td>115±4</td>
<td>110±5*</td>
</tr>
<tr>
<td></td>
<td>PMP after estradiol</td>
<td>113±3§</td>
<td>111±4</td>
<td>112±5</td>
<td>103±61§</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>Pre-MP</td>
<td>64±2</td>
<td>63±2</td>
<td>62±2</td>
<td>62±2</td>
</tr>
<tr>
<td></td>
<td>PMP before estradiol</td>
<td>68±3</td>
<td>65±3</td>
<td>67±3</td>
<td>68±4</td>
</tr>
<tr>
<td></td>
<td>PMP after estradiol</td>
<td>64±2§</td>
<td>62±2</td>
<td>64±3</td>
<td>63±3§</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>Pre-MP</td>
<td>77±1</td>
<td>76±2</td>
<td>75±2</td>
<td>74±2*</td>
</tr>
<tr>
<td></td>
<td>PMP before estradiol</td>
<td>85±3</td>
<td>82±3</td>
<td>83±3</td>
<td>82±4</td>
</tr>
<tr>
<td></td>
<td>PMP after estradiol</td>
<td>80±2§</td>
<td>78±3</td>
<td>80±3</td>
<td>76±4</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>Pre-MP</td>
<td>59±2</td>
<td>58±2</td>
<td>67±3*</td>
<td>83±5‡</td>
</tr>
<tr>
<td></td>
<td>PMP before estradiol</td>
<td>58±3</td>
<td>59±3</td>
<td>62±3</td>
<td>72±4†</td>
</tr>
<tr>
<td></td>
<td>PMP after estradiol</td>
<td>58±3</td>
<td>57±3</td>
<td>61±3</td>
<td>72±4†</td>
</tr>
</tbody>
</table>

Values are means±SE.

PMP indicates postmenopausal; Pre-MP, premenopausal.

*P<0.05.
†P<0.01.
‡P<0.001 vs baseline value.
§P<0.05.
||P<0.01.
In premenopausal subjects, plasma renin (P<0.05), and aldosterone (P<0.001) increased significantly in response to LBNP –40 mm Hg. A further elevation of aldosterone (P<0.001) was detected in the recovery phase. In contrast, in postmenopausal subjects these components of the RAS were not stimulated by LBNP before estradiol, and renin and aldosterone responses to LBNP were not affected by estradiol. However, compared with the pre-estradiol response, postestradiol angiotensin II values were significantly higher during all stages of LBNP (P<0.05), and a significant increase above these higher baseline values was observed at the end of LBNP (from 13±2 to 22±2 pmol/L; P<0.05). Aldosterone also increased above baseline values during recovery from LBNP –40 mm Hg (P<0.05), but this response was not augmented by estradiol (Table 3).

**Discussion**

This is the first study to our knowledge in healthy normotensive postmenopausal women to investigate hemodynamic and RAS responsiveness to acute reflex stimulation by simulated orthostatic stress, both before and after chronic administration of oral estradiol, and to compare these responses to reference values derived from healthy young premenopausal women studied under identical experimental conditions. Our hypothesis that any estradiol induced activation of the RAS would result in higher BP before and during LBNP was effectively refuted by this experiment. Our novel findings were: (1) compared with premenopausal women, HR responses to hypotensive LBNP tended to be impaired in these healthy postmenopausal women, and reflex activation of renin and angiotensin II was absent; (2) these blunted acute HR and renin responses to LBNP were not restored by 1 month of estradiol, whereas LBNP evoked a significant increase in angiotensin II concentrations on ERT; (3) estradiol increased resting angiotensinogen, plasma renin activity, and angiotensin II but not aldosterone; and (4) this increase in angiotensin II did not result in higher BP either at rest or with LBNP. On
Consistent with previous studies, postmenopausal estrogen therapy was associated with increased plasma concentrations of angiotensinogen and angiotensin II when measured during supine rest. The principal new finding of the present study was the discordance between the effects of estradiol on the vasoconstrictor, angiotensin II, and on BP. When subjects were receiving estradiol, BP was significantly lower at both rest and during LBNP – 40 mm Hg. Furthermore, there was no corresponding augmentation of the acute aldosterone or reflex HR responses to hypotensive LBNP on the estrogen study day. Taken together, these new findings suggest that when administered to healthy postmenopausal women, exogenous oral estradiol induces chronic net RAS activation characterized by an increase in plasma angiotensin II, but its actions may be counteracted by downregulation of vasoconstrictor, autonomic, or adrenocortical responsiveness to this peptide.

Differences in age and menopausal status are 2 factors that may contribute to impaired baroreflex modulation of HR and activation of the RAS. In men, aging is associated with an attenuated HR response to hypotensive LBNP. Although previous studies have shown that increased age is associated with reduced plasma concentrations of renin and aldosterone, its effect on angiotensin II and ACE1 activity have been less well-documented. Age is associated with an impaired capacity to respond to acute RAS stimuli, such as volume depletion and upright posture. However, recent studies suggest that whereas the plasma RAS system is possibly downregulated with age, the tissue RAS and/or end-organ responsiveness to the RAS may be upregulated, thus contributing to the pathophysiology of cardiovascular disease in aging populations.

Estrogen has previously been shown to improve baroreflex function in animal and human studies. Interestingly, in rodents, estrogen enhanced baroreflex-mediated bradycardia but did not influence baroreflex tachycardia in response to pharmacological stimuli. In the present study, despite similar baseline resting HR, the reflex HR response to hypotensive LBNP tended to be less in the postmenopausal women and was not restored by chronic estrogen treatment. Taken together, the results of the present study suggest that age, or other factors related to menopausal status but independent of estrogen status, may contribute to the differences in hemodynamic and RAS responsiveness to acute baroreflex stimulation observed between the premenopausal and postmenopausal women.

Chronic oral estrogen administration may induce relative resistance to the hemodynamic effects of angiotensin II via a variety of different mechanisms. For example, most of the well-described biological actions of angiotensin II are mediated by the angiotensin II type 1 (AT1) receptor. Recent studies have shown that estrogen status may directly influence AT1 receptor expression and transduction. A study in the spontaneously hypertensive rat model demonstrated increased vascular free radical production and enhanced angiotensin II-induced vasoconstriction after ovariectomy mediated via increased tissue expression of the AT1 receptor. Conversely, studies in animals have shown that administration of estrogen after ovariectomy downregulates AT1 receptor expression via post-transcriptional modulation of the 5' leader sequence RNA-binding proteins in vascular smooth muscle cells, the hypothalamus, adrenal cortex, and the kidney. Estrogen may also upregulate expression of the angiotensin II type 2 (AT2) receptor, which is re-expressed in response to injury and may exert cardiovascular effects opposite to those of the AT1 receptor. Thus, by altering the AT1/AT2 receptor balance, estrogen may induce resistance to the well-recognized hemodynamic effects of angiotensin II.

Estrogen may also attenuate hemodynamic responsiveness to angiotensin II via post receptor hypotensive counter-regulatory mechanisms. For example, exogenous estrogen increases nitric oxide bioavailability via both genomic and nongenomic mechanisms. The nitric oxide vasodilatory pathway downregulates AT1 receptor expression in vascular tissue and adrenal glands. Other angiotensin-related peptides, formed from angiotensinogen proteolysis, are being recognized for their biological activity by Brosnihan et al that administration of estrogen to female oophorectomized transgenic hypertensive (Ren2) mice increased levels of angiotensin-(1–7), decreased levels of ACE, and reduced the pressor response to angiotensin II. These authors suggested that estrogen may protect against hypertension by amplifying the vasodilator contributions of angiotensin-(1–7) while reducing the vasoconstrictor actions of angiotensin II.

Previous studies have shown that high estrogen levels are associated with downregulation of ACE. A decline in ACE activity may induce a degree of resistance to activation of the circulating RAS via reduced degradation of bradykinin, a potent vasodilator. Downregulation of ACE would be anticipated to reduce circulating angiotensin II. However, this was not the case in the present study, and previous studies have shown a reduction in ACE activity but an increase in angiotensin II after estrogen.

Angiotensin II, the principal regulator of aldosterone synthesis and secretion, augments enzymatic regulation at early and late stages of the aldosterone biosynthetic pathway via activation of the AT1 receptor in the adrenal cortex. Although there is usually good correlation between plasma angiotensin II and aldosterone levels, aldosterone and angiotensin II can be dissociated under certain conditions. Recent studies in rodents have shown that estrogen-induced down-regulation of AT1 receptor expression in the pituitary and adrenal glands is associated with attenuated pituitary corticotropic and adrenal aldosterone responses to angiotensin II. Angiotensin II levels in the adrenal gland have also been shown to feedback to influence adrenal AT1 receptor expression, and thus to influence the aldosterone response to circulating angiotensin II. Wu et al have recently shown that estrogen therapy may reduce adrenal AT1 receptor expression indirectly by modulating adrenal levels of angiotensin II, either by inhibiting adrenal angiotensin II synthesis (via lowering local ACE activity) or, alternatively, by preventing adrenal uptake of angiotensin II from the circulating system through receptor-mediated mechanisms.

High circulating levels of estrogen from endogenous and exogenous sources have been shown to influence neurogenic...
mechanisms of BP regulation. For example, sympathetic nervous system activity is attenuated in premenopausal women during the high versus low estrogen phase of the menstrual cycle, and in postmenopausal women after exogenous estrogen therapy. Thus, in the present study, the lower BP of postmenopausal subjects when using estradiol may reflect an inhibitory action on central sympathetic outflow.

**Perspectives**

Overactivity of the RAS has been implicated in the pathogenesis of hypertension, congestive cardiac failure, coronary and cerebral atherosclerosis, and progressive renal disease. The results of the present study suggest that estrogen may protect against activation of the RAS directly at the receptor level or alternatively by upregulating counter-regulatory post-receptor hypertensive mechanisms. However, these findings were derived from healthy normotensive postmenopausal women. In contrast, ERT may have potentially deleterious effects in women with conditions (such as hypertension and atherosclerosis) that are characterized by both an increase in angiotensin II and a concurrent impaired capacity to recruit hypertensive and cardioprotective mechanisms necessary to attenuate or counteract the adverse effects of this potent vasoactive hormone. Better understanding of the complex interactions between sex, estrogen, progesterone, menopause, the RAS, and baroreflex mechanisms of BP regulation may provide insight into the pathogenesis of cardiovascular diseases in women and the conflicting reports of the effects of ERT on BP while also facilitating the development of optimal sex-specific cardiovascular disease prevention and therapeutic strategies. It may also assist in explaining the adverse cardiovascular outcomes reported in recent trials of hormone replacement therapy.

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**References**

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