Abstract. It has been demonstrated elsewhere that circulating renin angiotensin system (RAS) components peak when plasma estrogen levels are highest, during the luteal phase of the normal menstrual cycle. This phenomenon has been attributed to “activation” of the RAS. The end-organ vasoconstrictive response to this phenomenon has not been well established. In two related experiments, the RAS was studied in healthy, premenopausal women during predefined phases of the normal menstrual cycle. In the first experiment, the circulating components of the RAS and the systemic hemodynamic response to incremental lower body negative pressure (LBNP) during the follicular and luteal phases of the menstrual cycle were examined. Response variables included mean arterial pressure (MAP), renin, plasma renin activity (PRA), angiotensin II (AngII), and aldosterone. Baseline levels of renin, PRA, and aldosterone were significantly higher in the luteal phase. In response to LBNP, there were significant increases in all variables in both phases; however, the humoral response to this stimulus was significantly augmented in the luteal phase compared with the follicular phase. Despite these elevations in circulating components of the RAS during the luteal phase, subjects were unable to maintain MAP in response to LBNP, exhibiting a dramatic depressor response that did not occur during the follicular phase. In the second experiment, renal and peripheral hemodynamic function at baseline, and in response to AngII blockade with losartan, were examined in women during these high and low estrogen phases of the menstrual cycle. The renal and peripheral hemodynamic responses were similar in the luteal phase and the follicular phase. These results demonstrate that, despite an increase in circulating RAS components during the luteal phase of the menstrual cycle, the system is blunted rather than “activated,” at least at a tissue level. Further studies are needed to clarify this mechanism.

It is well known that angiotensinogen expression is transcriptionally regulated by estrogen (1) and that high endogenous estrogen levels increase circulating renin angiotensin system (RAS) components. In normal women, angiotensin II (AngII) and plasma renin activity (PRA) are elevated during the luteal phase of the menstrual cycle (2–5). Because of the known role played by the RAS in progression of chronic renal disease (6–9), it has been difficult to reconcile estrogen-mediated increases in circulating RAS components with the knowledge that female gender protects against the progression of renal disease (10). But activation of the RAS consists not only of a humoral response—the increased generation of RAS components—but also a tissue response—end-organ vasoconstriction. This aspect of the RAS in women has been less well studied but is essential to our understanding of estrogen-mediated RAS activation.

We examined this component in two related experiments. In the first experiment, we used incremental lower body negative pressure (LBNP), a known activator of the RAS (11,12), to study both the generation of RAS components and systemic hemodynamic responsiveness during the follicular and luteal phases of the menstrual cycle. We hypothesized that the hemodynamic response to RAS stimulation could clarify the activity of the system, with maintenance of arterial pressure signifying normal end-organ responsiveness to RAS stimulation and a depressor response signifying blunting. In a related experiment, we examined the renal and peripheral vasodilator response to AngII blockade during different phases of the menstrual cycle in 20 premenopausal, normotensive women. We hypothesized that the activity of the RAS would be reflected by the hemodynamic response to the AngII receptor blockade, with an augmented renal and systemic depressor response during the luteal phase suggesting normal RAS responsiveness and a lesser response signifying blunting (13,14).

Materials and Methods

Study 1 Protocol

The study was performed with the approval of the University of Toronto Human Subjects Review Committee and with the informed written consent of each subject. Ten healthy, nulliparous premenopausal women were recruited to participate. Mean age was 28 ± 1 yr. All subjects were normotensive, nonobese, nonsmokers, and nonusers of oral contraceptive medications. Women were excluded if they had evidence of anovulatory cycles—irregular menses or cycles >28 d. Pregnancy was ruled out by a negative serum β-human chorionic gonadotropin test before enrollment. None of the subjects were ingesting any regular medications. They were studied between the third
and the sixth day after the onset of menstruation, which represented the follicular phase. Ovulation was calculated as day 13 to 15, and women were studied by use of an identical protocol between days 15 and 24. Blood was drawn for 17β-estradiol and progesterone at each phase. All subjects were counseled to adhere to a diet that maintained their normal caloric intake, sodium intake of >150 mmol/d, and protein intake of 1 to 1.5 g/kg per d for 7 d before the study. Compliance was assessed by measurement of sodium and urea excretion in a 24-h urine sample collected 1 d before the study. Protein intake of 1 to 1.5 g/kg per d for 7 d before the study.

Study 2 Protocol

Twenty nulliparous women with similar demographic characteristics were recruited for this study. Ten women were studied during the luteal phase of the menstrual cycle, and 10 were studied during the follicular phase. After identical prestudy enrollment and preparation procedures, they presented to the Renal Physiology Laboratory on the day of testing.

An 18-gauge peripheral venous cannula was inserted into the antecubital vein for infusions of inulin and para-aminohippurate (PAH), and another cannula was placed in the opposite arm for blood sampling. Each subject was instructed to void and then to drink sufficient water in the first 45 min to induce a water diuresis. Approximately 200 ml of water were ingested in each hour of the protocol to maintain an adequate urine output for collection of spontaneously voided samples. Baseline blood samples were collected for $P_{\text{NOX}}$, 17β-estradiol, progesterone, inulin blank, and hematocrit (HCT), and urine was collected for inulin blank. Hemodynamic parameters (mean arterial pressure [MAP], heart rate) were measured throughout the study by automated sphygmomanometer (Dinamapp) and were recorded during each half-hour of the protocol. Renal hemodynamics were measured by use of inulin and PAH clearance techniques, as described elsewhere (5,13,14). Three timed urine collections of 20 min duration each were obtained for determination of baseline GFR and effective renal plasma flow (ERPF). At the end of this period, losartan (Cozaar; Merck, Sharpe, and Dohme, Canada) was administered at a subdepressor dose of 25 mg (13,14). During each hour, for a total of 3 h, blood was collected for PRA, inulin, PAH, and HCT, and urine was collected for inulin, PAH, and urine sodium excretion (UNaV).

Sample Collection and Analytic Methods

Blood samples that were collected for assay of $P_{\text{NOX}}$ were immediately centrifuged at 3000 rpm for 10 min at 4°C. Plasma was separated, placed on ice, and then stored at −70°C before the assay. The assay involved the enzymatic conversion of all nitrate to nitrite by the enzyme nitrate reductase. The detection of total nitrite was then determined as a colored azo dye product of the Griess reaction (15).

Blood samples that were collected for inulin and PAH determinations were immediately centrifuged at 3000 rpm for 10 min at 4°C. Plasma was separated, placed on ice, and then stored at −70°C before the assay. Inulin concentrations in plasma and urine were measured by a modified method of Walser et al. (16), and PAH concentration was measured by a spectrophotometric method according to Brun (17). The mean of the final two clearance periods represented GFR and ERPF, expressed per 1.73 m². Filtration fraction (FF) represented the ratio of GFR to ERPF. Renal blood flow (RBF) was calculated by dividing the ERPF by (1 − HCT). Renal vascular resistance (RVR) was derived from the ratio of MAP to RBF.

Urinary sodium concentration was measured by a flame photometry method. AngII was measured by RIA. Blood was collected into pre-chilled tubes that contained ethylenediaminetetraacetate (EDTA) and angiotensinase inhibitor (0.1 ml Bestatin Solution; Buhlmann Laboratories AG, Switzerland). After centrifugation, plasma samples were stored at −70°C until analysis. On the day of analysis, plasma samples were extracted on phenylsilysilica columns. A competitive RIA kit supplied by Buhlmann Laboratories AG was used to measure the extracted AngII. Aldosterone was measured by RIA, by use of the Coat-A-Count system. Active plasma renin was measured by a two-site immunoradiometric assay in which two 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 (18).

Statistical Analyses

All statistical analyses were performed by use of the statistical package SAS (SAS Institute Inc., Cary, NC). Data are presented as mean ± SEM. $P \leq 0.05$ was considered statistically significant. In study 1 (LBNP study), between-phase and within-group baseline differences and differences in the response to LBNP were determined by repeated-measures ANOVA with Bonferroni’s correction. In study 2 (losartan study), the differences between groups at baseline were determined by use of nonparametric methods (Wilcoxon rank sums). Within-subject and between-group differences in the response to losartan were determined by repeated-measures ANOVA and Bonferroni’s correction. Correlation coefficients were used to discern any relationships between 17β-estradiol plasma concentrations and the renal and peripheral response to AngII blockade.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the subjects who participated in studies 1 and 2. There were no significant differences between the phases of the menstrual cycle, except
for estrogen and progesterone levels that were appropriate to the phase of the menstrual cycle being studied. No significant difference was detected in \( \text{P}_{\text{NOX}} \) levels between phases of the menstrual cycle or between groups.

**Response to LBNP in Follicular and Luteal Phase**

The responses of renin, AngII, aldosterone, and MAP during the follicular and luteal phase of the menstrual cycle are shown in the Figures 1 through 4. During the luteal phase, compared with the follicular phase, significant increases were observed in baseline renin (28 ± 5 \( \mu \text{U/ml} \) in the luteal phase versus 11 ± 2 \( \mu \text{U/ml} \) in the follicular phase, \( P = 0.005 \)), PRA (2 ± 0.2 \( \mu \text{g AngI/L per min} \) versus 0.4 ± 0.1 \( \mu \text{g AngI/L per min} \), \( P = 0.03 \)), and aldosterone (241 ± 36 pmol/L versus 105 ± 19 pmol/L, \( P = 0.02 \)). There was no significant difference in AngII levels between phases (11 ± 2 pg/ml versus 9 ± 2 pg/ml; \( P = 0.5 \)). The generation of RAS com-

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**Table 1. (LBNP Study) Subjects who participated in studies 1 and 2**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Follicular Phase</th>
<th>Luteal Phase</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower body negative pressure study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (yr)</td>
<td>28 ± 1</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22 ± 0.9</td>
<td>23 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>79 ± 2</td>
<td>78 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>( \text{UnaV} ) (mmol/d)</td>
<td>159 ± 11</td>
<td>182 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>corrected ( \text{Una} ) (mmol/kg per d)</td>
<td>2.7 ± 0.2</td>
<td>3 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>protein intake (g/kg per d)</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>17( \beta )-estradiol (pmol/L)</td>
<td>83 ± 13</td>
<td>276 ± 14</td>
<td>0.006</td>
</tr>
<tr>
<td>progesterone (nmol/L)</td>
<td>0.86 ± 0.1</td>
<td>25 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>( \text{P}_{\text{NOX}} ) (( \mu \text{mol/L} ))</td>
<td>52 ± 5</td>
<td>60 ± 18</td>
<td>NS</td>
</tr>
</tbody>
</table>

| **Losartan study** | | | |
| age (yr) | 28 ± 1 | 27 ± 1 | NS |
| BMI (kg/m\(^2\)) | 22 ± 0.9 | 22 ± 1 | NS |
| MAP (mmHg) | 82 ± 2 | 79 ± 1 | NS |
| \( \text{UnaV} \) (mmol/d) | 151 ± 8 | 167 ± 16 | NS |
| corrected \( \text{Una} \) (mmol/kg per d) | 2 ± 0.2 | 2 ± 0.4 | NS |
| protein intake (g/kg per d) | 1 ± 0.07 | 1 ± 0.08 | NS |
| 17\( \beta \)-estradiol (pmol/L) | 80 ± 19 | 351 ± 20 | 0.0001 |
| progesterone (nmol/L) | 0.78 ± 0.1 | 32 ± 4 | 0.0001 |
| \( \text{P}_{\text{NOX}} \) (\( \mu \text{mol/L} \)) | 55 ± 12 | 44 ± 6 | NS |

\( ^a \)BMI, body mass index; MAP, mean arterial pressure; \( \text{UnaV} \), urine sodium excretion; \( \text{P}_{\text{NOX}} \), oxidation products of nitric oxide.

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**Figure 1.** Response of renin to incremental lower body negative pressure (LBNP) during the follicular phase (■) and the luteal phase (▲) of the normal menstrual cycle. *\( P < 0.05 \) versus baseline; §§\( P < 0.05 \) versus response during the follicular phase.

**Figure 2.** Response of angiotensin II (AngII) to incremental LBNP during the follicular phase (■) and the luteal phase (▲) of the normal menstrual cycle. *\( P < 0.05 \) versus baseline; §§\( P < 0.05 \) versus response during the follicular phase.
versus 0.05 mmol/L, P vs baseline; §P < 0.05 versus response during the follicular phase.

Figure 3. Response of aldosterone to incremental LBNP during the follicular phase (■) and the luteal phase (▲) of the normal menstrual cycle. *P < 0.05 versus baseline; §P < 0.05 versus response during the follicular phase.

Response to AngII Blockade in Follicular and Luteal Phase

PRA levels increased from baseline in both groups consistent with AngII receptor blockade. In the group studied during the luteal phase, the baseline value was 0.36 ± 0.1 ng AngII/L per min and increased to 1.2 ± 0.1 by the end of third hour (P = 0.013). In the group studied during the follicular phase, the baseline value was 1.8 ± 0.2 ng AngII/L per min and increased to 3.5 ± 0.3 by the end of the third hour (P = 0.025). The renal and systemic hemodynamic responses to AngII blockade did not differ between the follicular and luteal phases. Results are shown in Table 2. There were no significant correlations between 17β-estradiol levels and baseline GFR (r = 0.14, P = 0.54), the GFR response to AngII blockade (r = 0.36, P = 0.13), baseline ERPF (r = 0.14, P = 0.55), the ERPF response (r = 0.21, P = 0.6), baseline FF (r = 0.23, P = 0.26) the FF response (r = 0.05, P = 0.8), baseline MAP (r = 0.18, P = 0.45), or the MAP response (r = 0.13, P = 0.6).

Discussion

In this series of experiments, we studied the hemodynamic impact of elevated circulating RAS components in healthy normotensive women during the follicular and luteal phases of the menstrual cycle. Our rationale was that, although the luteal phase is characterized by elevations in plasma RAS components, the end-organ response has not been examined, and the system as a whole during the menstrual cycle is poorly understood. Our study confirmed reports elsewhere of elevated levels of renin, PRA, and aldosterone in the luteal phase of the menstrual cycle compared with the follicular phase, despite equivalent arterial pressure, which suggests humoral RAS activation. Our key findings were (1) LBNP caused a significant increase in all RAS components during both phases of the cycle, but this humoral response was significantly augmented during the luteal phase; (2) despite the increased generation of RAS components, women in the luteal phase were unable to maintain MAP during incremental LBNP; and (3) despite apparent humoral RAS activation, the vasodilatory response to AngII blockade was not augmented in the luteal phase.

Several groups have demonstrated that circulating components of the RAS are elevated during the luteal phase of the menstrual cycle (2–5). In animal models, estrogen induces increased levels of PRA (2,19). Sealey et al. (3) studied women in different phases of the menstrual cycle as they underwent ovarian stimulation for in vitro fertilization and found that levels of PRA and urinary excretion of aldosterone were sig-
sificantly increased during the luteal phase of the menstrual cycle compared with other phases. Furthermore, a significant positive correlation existed between levels of these RAS components and estrogen. Similarly, Chapman et al. (4) studied women during various phases of the menstrual cycle and found that there was an increase in PRA and aldosterone in the luteal phase compared with the follicular phase, and a recent study from our laboratory produced comparable results (5). Chapman et al. (4) have attributed this change to RAS activation. On careful examination, it is apparent that the elevated circulating RAS components may have little vasoconstrictive impact. Chapman et al. (4) measured peripheral vascular resistance in women in the luteal phase and found it to be reduced, and a study from our laboratory noted that in high estrogen states the vasoconstrictive response to infused AngII is blunted (5). This study is the first to examine the RAS and peripheral hemodynamic function in response to dynamic maneuvers during the normal menstrual cycle. Despite evidence of humoral RAS activation during the luteal phase, during LBNP at ~40 mmHg, women experienced a significant decline in MAP, which is normally maintained by sympathetic nervous system and RAS activation (20), and there was no difference between phases of the menstrual cycle in the vasodilatory response to losartan, despite adequate AngII blockade. These findings are suggestive of downregulation of the tissue response to increased levels of AngII.

There are several possible mechanisms that may help explain this phenomenon. It is known that high levels of estrogen in the luteal phase stimulate endothelial nitric oxide (NO) synthase (21–23), producing a vasodilatory effect (24), and that NO can downregulate AngII type I receptors in vascular tissue (25) and adrenal glands (26) and mitigate the actions of AngII. This phenomenon may have impaired the ability to maintain MAP in response to LBNP (27). Although, similar to the findings of Chapman et al. (4), we were unable to detect a difference in P\textsubscript{NOX} levels between the phases of the menstrual cycle, we cannot eliminate the possibility that alterations in NO production caused the blunting of the AngII response. Not only were our numbers small, allowing us to detect only major differences, but we did not place subjects on a low-nitrate diet before study. In addition, it has been suggested by Schmidt et al. (28) that blood and urine measurements of NO as indices of NO activity are of limited utility in humans, even when measured under optimum conditions. Therefore, we cannot exclude the counterregulatory effects of NO as a factor influencing our findings.

Other possibilities exist. In ovariectomized female rats, estrogen decreases AT1 receptor expression in adrenal and pituitary tissue through modulation of 5' leader sequence RNA-binding proteins (29), which suggests that high levels of estrogen in the luteal phase may downregulate AngII receptor expression, thereby limiting the binding and subsequent activation of AngII. In addition, estrogen downregulates AT1 receptor expression in vascular smooth-muscle cells, an effect that could account at least in part for the decline in systemic BP during LBNP in the luteal phase (30). Another possibility is that progesterone levels affected on our results. This hormone is highest in the luteal phase and lowest in the ovulatory phase (31) because it competes with mineralocorticoid for the type I corticosteroid receptor in the kidney (31–33). Although levels of aldosterone are increased in the luteal phase, high levels of progesterone may be mitigating the effect of aldosterone through competitive antagonism in the kidney. Any of these mechanisms could account for the observed responses, but they remain hypothetical.

We could find no evidence of baseline renal or peripheral vasodilatation in the luteal phase. This result is in contrast to that of Chapman et al. (4) and others (34–36), who noted an increase in GFR and RBF during the luteal phase. This finding, is, however, not universal, because other investigators (37–39) who have used equally valid methods of assessing renal func-

### Table 2. Losartan study results\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteal phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83 ± 2</td>
<td>81 ± 2</td>
<td>78 ± 1</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m(^2))</td>
<td>105 ± 7</td>
<td>105 ± 6</td>
<td>115 ± 9</td>
<td>114 ± 8</td>
</tr>
<tr>
<td>ERPF (ml/min per 1.73 m(^2))</td>
<td>618 ± 41</td>
<td>570 ± 33</td>
<td>603 ± 48</td>
<td>656 ± 51</td>
</tr>
<tr>
<td>FF</td>
<td>0.17 ± 0.006</td>
<td>0.18 ± 0.005</td>
<td>0.19 ± 0.007</td>
<td>0.18 ± 0.008</td>
</tr>
<tr>
<td>RBF (ml/min per 1.73 m(^2))</td>
<td>1011 ± 66</td>
<td>923 ± 55</td>
<td>967 ± 76</td>
<td>1049 ± 81</td>
</tr>
<tr>
<td>RVR (mmHg/L per min)</td>
<td>85 ± 5</td>
<td>87 ± 4</td>
<td>86 ± 6</td>
<td>86 ± 5</td>
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<tr>
<td>Follicular phase</td>
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<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>82 ± 3</td>
<td>81 ± 3</td>
<td>79 ± 3</td>
<td>77 ± 3</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m(^2))</td>
<td>110 ± 7</td>
<td>111 ± 7</td>
<td>116 ± 7</td>
<td>106 ± 7</td>
</tr>
<tr>
<td>RPF (ml/min per 1.73 m(^2))</td>
<td>619 ± 40</td>
<td>630 ± 31</td>
<td>645 ± 32</td>
<td>607 ± 67</td>
</tr>
<tr>
<td>FF</td>
<td>0.18 ± 0.07</td>
<td>0.18 ± 0.06</td>
<td>0.18 ± 0.05</td>
<td>0.18 ± 0.01</td>
</tr>
<tr>
<td>RBF (ml/min per 1.73 m(^2))</td>
<td>969 ± 71</td>
<td>983 ± 61</td>
<td>1012 ± 65</td>
<td>946 ± 111</td>
</tr>
<tr>
<td>RVR (mmHg/L per min)</td>
<td>83 ± 5</td>
<td>83 ± 4</td>
<td>81 ± 5</td>
<td>82 ± 12</td>
</tr>
</tbody>
</table>

\textsuperscript{a} ERPF, effective renal plasma flow; FF, filtration fraction; RBF, renal blood flow; RVR, renal vascular resistance.
tion were unable to detect clinically significant renal hemodynamic differences in the phases of the menstrual cycle. The differences among these studies may be in prestudy preparation. It is well known that both sodium intake and protein consumption affect GFR (40,41). We controlled for this by confirming that our subjects were ingesting equivalent sodium and protein diets for the week before each study.

A more important observation, considering the primary objective of the study, was the absence of renal hemodynamic evidence of increased AngII activity (a decrease in RBF and an increase in FF). In an earlier study by Bisson et al. (42) in premenopausal women it was noted that, similarly, no differences in sodium excretion exist between the luteal and the follicular phase, despite apparent activation of the RAS. Taken together, these studies suggest that, although RAS components are significantly elevated in the presence of high levels of estrogen, the usual renal hemodynamic and excretory responses are attenuated, which suggests that the system is actually blunted rather than activated.

Potential confounding variables may have impacted on our results. To control for sodium depletion or protein overfeeding, both of which can result in increased activity of the RAS (43,44), each subject was counseled to adhere to a prescribed diet. As Table 1 demonstrates, there were no differences observed in the 24-h urinary excretion of sodium, and the calculated protein intake was similar. Furthermore, none of the subjects were ingesting any regular medications, including the oral contraceptive pill, which has been shown to affect RAS function (14,45). Our method of calculating phases of the menstrual cycle consisted of counting days after the onset of menstruation. Although the possibility exists that some inaccuracies may have resulted, we controlled for this by excluding women from the study who had irregular menses and/or a cycle longer than 28 d and by measuring estrogen and progesterone levels at each phase of the menstrual cycle. The significant elevation in progesterone levels in the luteal phase attests to the accuracy of the method.

In summary, this series of related experiments provides evidence that, although women exhibit humoral evidence of activation of the RAS in the luteal phase of the menstrual cycle, there is little evidence of a tissue response. Not only is the ability to maintain arterial pressure in the face of simulated orthostatic stress impaired in this phase, the vasodilatory response to AngII blockade is not enhanced. Taken together, these experiments suggest that, despite the increased generation of RAS components, which suggests RAS activation, the system may actually be downregulated in high-estrogen states. Any blunting of the growth-promoting properties of AngII cannot be discerned from our present data, but it is tempting to speculate that estrogen may also modulate this aspect of the AngII response. This hypothesis provides a plausible mechanism by which estrogen, while increasing RAS components, may defend against the deleterious effects of AngII by down-regulating tissue responsiveness, either by a direct effect on receptors or through the counterregulatory impact of NO.

Acknowledgments
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