Acute Gender-Specific Hemodynamic and Inotropic Effects of 17β-Estradiol on Rats

Martin E. Beyer, Georg Yu, Hartmut Hanke, Hans Martin Hoffmeister

Abstract—Estrogen has cardioprotective effects. In addition to beneficial effects on lipid metabolism, estrogen affects the vascular tone and may reduce endothelial dysfunction. In the present study, we examined acute gender-specific hemodynamic and inotropic effects of 17β-estradiol (17β-E) versus the control situation in open-chest rats. In addition to measurements in the intact circulation, myocardial function was examined on the basis of isovolumic registration independent of peripheral vascular effects. Regarding the dose-dependent and gender-specific effects of 17β-E, in female rats, 17β-E (50, 100, or 200 ng/kg) increased cardiac output (CO) (26%, 43%, and 59% versus control animals) as a result of reduction in total peripheral resistance (TPR) (−13%, −18%, and −24%) without any effect on myocardial contractility (isovolumic left ventricular systolic pressure, −1%, 0%, and −6%). These vascular effects are less pronounced in male rats (for 200 ng/kg 17β-E: CO, 34%; TPR, −14%). We investigated gender-specific effects of 200 ng/kg 17β-E after pretreatment with the estrogen receptor (ER) antagonist ICI 182,780. ER blockade reduced the effects of estrogen in female rats (CO, 29%; TPR, −17%) and male rats (CO, 19%; TPR, −11%). Regarding the effects of 200 ng/kg 17β-E after pretreatment with Nω-nitro-L-arginine methyl ester, NO synthesis inhibition completely prevented the acute vascular effects of estrogen in female rats (CO, −4%; TPR, 1%). In addition, immunohistochemical staining revealed no gender-specific differences of the vascular ER distribution. 17β-E caused an acute dose-dependent and gender-specific reduction in the afterload. ERs are involved in both genders in this vasodilative effect that is mediated by NO. This NO-mediated effect may explain in part the cardioprotective effect of estrogen. (Hypertension. 2001;38:1003-1010.)

Key Words: estrogen receptors, estrogen nitric oxide hemodynamics contractility rats, Wistar

The incidence of coronary heart disease (CHD) is significantly lower in women than in men1 and increases in women after surgically induced menopause2 or after natural menopause.3 Postmenopausal estrogen replacement therapy is a protective factor in the development of CHD.4 Studies in primates have shown that estrogen therapy has a protective effect against atherosclerotic plaque development,5,6 which cannot be fully explained by the beneficial effects of estrogen on lipid metabolism.1 Estrogen also affects vascular tone.7 Arterial tone is also of importance in the pathogenesis of atherosclerosis: in humans with CHD, there is an abnormal coronary vasoconstriction in response to acetylcholine (called endothelial dysfunction).8 17β-Estradiol (17β-E) treatment9 and endogenous estrogen10 enhance endothelium-dependent relaxation in response to acetylcholine, and animal11,12 studies have demonstrated that estrogen can modulate or even abolish endothelial dysfunction in atherosclerotic vessels. This effect of 17β-E was detectable only in atherosclerotic coronary arteries from women, not in those from men.12 Short-term estrogen administration has beneficial effects on exercise-induced myocardial ischemia in women with CHD.13 Because short-term administration of estrogen causes vasodilation,14 it seems possible that estrogen has a direct effect on the vasculature. Animal15 and human16,17 studies suggest that this estrogen-induced vasorelaxation may be mediated by NO. Estrogen treatment causes an induction of the neuronal and the endothelial NO synthase in animals.18 In addition, calcium antagonistic properties may contribute to the cardioprotective effect of estrogen, because studies on isolated cardiac myocytes demonstrated a calcium-antagonistic effect of 17β-E.19 These calcium-antagonistic properties may cause undesirable cardiodepressant effects. Furthermore, antioxidative properties of estrogen20 may have cardioprotective effects.

In the present study, we examined the hemodynamic and inotropic effects of 17β-E under different conditions in an open-chest animal model that has been previously described.21,22 In addition to measurements in the intact circulation, this model permits quantification of the left ventricular pressure–generating capacity to determine myocardial effects independent of preload and afterload conditions (isovolumic left ventricular pressure [peak LVSP] and peak first deriva-
tive of left ventricular pressure [peak dP/dt max] as indices of myocardial contractility). In the first part of the study, we investigated the dose-dependent effects of 17β-E in female rats and gender-specific differences from male rats. Estrogen receptors (ERs) are detectable in blood vessels23 and play a role in the regulation of endothelial NO production.24 Thus, in the second part of the study, we examined the gender-specific significance of ERs for the hemodynamic effects of 17β-E, which was administered after selective ER blockade by the pure estrogen antagonist ICI 182,780.25 In the third part of the study, we examined whether the acute vascular effects of 17β-E were mediated by NO. Therefore, hemodynamic effects of 17β-E were investigated after NO synthesis inhibition by N^G^^-nitro-L-arginine methyl ester (L-NAME).26 In addition, the vascular ER distribution in the descending aorta was determined in female and male animals by immunohistochemical staining.

## Methods

### Hemodynamic and Inotropic Measurements

The hemodynamic experiments were performed on 4-month-old normotensive fertile Wistar rats. The procedure was previously described in detail.2,21

17β-E (Sigma Chemical Co), dissolved in DMSO (Fluka Chemie AG), was diluted with 0.9% NaCl to a 1.6×10^{-3}% DMSO solution with a final volume of 1 mL. The control group received 1 mL of this DMSO solution without 17β-E. The dose-dependent effect in female rats was investigated by the administration of 50, 100, or 200 ng/kg 17β-E and comparison with the control situation. In male rats, 200 ng/kg 17β-E was used as a comparison with the control situation. At 12 minutes after preparation, control data for auxotonic and isovolumic measurements were obtained. Three minutes later, we started the intravenous drug infusion for 7 minutes. Auxotonic measurements were recorded every minute during infusion and at 5, 10, and 15 minutes after termination of infusion. At termination of infusion and 5 and 15 minutes later isovolumic measurements were performed. To examine the gender-specific effects of 200 ng/kg 17β-E after ER blockade, for 7 minutes, we infused 1 mg/kg ICI 182,780 (Tocris Cookson Ltd), dissolved in 1 mL of a 1.6% DMSO solution. At 10 minutes later, preinfusion control data were recorded, and after an additional 3 minutes, the 17β-E or control infusion was started. The following procedure was identical to that of the previous experiments. To study the role of NO on the estrogen-mediated effects, female animals were pretreated with an intravenous bolus injection of 100 μg/kg concentration of the NO synthesis inhibitor L-NAME (Sigma Chemical Co), diluted in 1 mL of 0.9% NaCl. At 45 minutes later, experiments with 200 ng/kg 17β-E versus the control situation were started according to the previous protocol.

### Determination of 17β-E Plasma Levels

At 15 minutes after termination of the infusion, blood samples were withdrawn, collected in EDTA-containing tubes, and centrifuged at 3000 rpm at 4°C for 10 minutes. 17β-E plasma levels were measured with commercial RIA kits (Biermann Inc).

### Immunohistological Detection of ERs

At the end of control experiments from 6 female and 6 male rats, the descending aorta was excised for immunohistological detection of ERs in the arterial vessel wall. The procedure for immunohistochemical staining of ERs and cell nuclei was previously described in detail.27 Histological sections were examined by an independent investigator blinded for the type of arterial segments, who used a fluorescent microscope. The percentage of ER-positive cells was calculated by counting ER-positive cells in relation to the total cell number indicated by cell nuclei staining in identical sections of 8 diametrically arranged segments of an ocular grid. Analysis was performed separately with respect to endothelial and vascular smooth muscle cells.

### Statistical Analysis

Data are expressed as mean±SEM. Hemodynamic data were normalized to individual preinfusion control data (100% at the beginning of

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### Table 1. Hemodynamic Measurements in the Intact Circulation and Isovolumic Registrations Without Pretreatment or After Pretreatment With ICI 182,780 or L-NAME at the Beginning of Infusion of 1 mL Control Solution or of 17β-E

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Pretreatment Female Rats</th>
<th>No Pretreatment Male Rats</th>
<th>ICI 182,780 Female Rats</th>
<th>ICI 182,780 Male Rats</th>
<th>L-NAME Female Rats</th>
<th>L-NAME Male Rats</th>
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<td>LVSP, mm Hg</td>
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<td>122.5±2.6‡</td>
<td>128.1±6.3</td>
<td>125.6±1.8§</td>
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<td>64.7±3.0*</td>
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<td>67.8±1.4</td>
<td>81.5±2.8†</td>
<td>71.6±3.5§</td>
<td>92.5±2.4‡</td>
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<td>6171±297∥</td>
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<td>247.9±8.0‡</td>
<td>238.8±11.7</td>
<td>293.7±14.4</td>
<td>381.4±52.3†</td>
<td>297.1±14.4</td>
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<tr>
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<td>298.8±11.7</td>
<td>293.7±14.4</td>
<td>381.4±52.3†</td>
<td>297.1±14.4</td>
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<td>SV, μL</td>
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<tr>
<td>Peak dP/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s</td>
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<td>9644±397∥</td>
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LVEDP indicates left ventricular end-diastolic pressure; AoP<sub>sys</sub>, diastolic aortic pressure; AoP<sub>d</sub>, mean aortic pressure; HR, heart rate; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; TPR, total peripheral resistance; peak LVSP and peak dP/dt<sub>max</sub> data derived from isovolumic maximum beat.

Values are mean±SEM.

*P<0.05, †P<0.01, ‡P<0.001 vs group of the same gender without pretreatment.

§P<0.05, ¶P<0.01, ††P<0.001 vs the groups with the same pretreatment but different gender.
At baseline LVSP, heart rate and dP/dt max were significantly higher in male rats than in female rats (Table 1). Table 2 shows the results of the hemodynamic measurements after 17β-E or control solution infusion in the intact circulation. During the 17β-E-infusion, the blood pressure increased. 17β-E increases the cardiac output (Figure 1A). 17β-E at 100 ng/kg has about the same effect in female rats as a double dose in male rats. Comparable effects can be shown for ejection fraction (Figure 1B). The calculated total peripheral resistance is reduced.

### Results

**Gender-Specific Hemodynamic and Inotropic Effects of 17β-E**

At baseline LVSP, heart rate and dP/dt max were significantly higher in male rats than in female rats (Table 1). Table 2
Results of the measurements are shown in Table 3. The short-lasting gender-independent increase in the pressures is less pronounced after ER blockade, and the chronotropic effect of 17β-E is completely abolished. The estrogen-induced increase in stroke volume is diminished by ICI 182,780 but still more pronounced in female rats (Figures 2A.1 and 2A.2). Due to decreased effects of 17β-E on stroke volume and heart rate after ER blockade, the estrogen effect on cardiac output is reduced ≈50% after ICI 182,780 infusion but still more pronounced in female rats (Figures 2B.1 and 2B.2). The gender-specific vasodilative effect of 17β-E is also reduced by ICI 182,780 (Figures 2C.1 and 2C.2).

17β-E also has no inotropic effect after ER blockade (Table 3).

**Hemodynamic and Inotropic Effects of 17β-E After Inhibition of NO Synthesis With L-NAME**

L-NAME increases the pressures in female rats (Table 1). To exclude the effects of L-NAME, we provide the results after 17β-E or control solution infusion in preinfusion values at 45 minutes after the injection of L-NAME when a steady state was obtained (Table 3).

After NO synthesis inhibition with L-NAME, the effect of 17β-E on the pressures is completely prevented. The 17β-E–mediated effects on ejection fraction, stroke volume (Figure 2A.3), and cardiac output (Figure 2B.3) are completely abolished, because L-NAME totally prevents the vasodilative effects of 17β-E (Figure 2C.3).

The indices of myocardial contractility (peak LVSP, peak dP/dt max) are not influenced by 17β-E after pretreatment with L-NAME (Table 3).

**17β-E Plasma Levels**

Figure 3 shows a dose-related increase in the 17β-E plasma levels but no gender-specific differences in plasma levels after the infusion of 200 ng/kg 17β-E. In neither female rats (17β-E 51.1 ± 4.1 pg/mL, control 26.8 ± 8.7 pg/mL; P < 0.05) nor male rats (17β-E 51.4 ± 10.3 pg/mL, P < 0.05) does ER blockade by ICI 182,780 have an effect on the 17β-E plasma levels compared with those of animals without ER blockade. Inhibition of NO synthesis by L-NAME also has no effect on 17β-E plasma levels: (17β-E 69.4 ± 22.9 pg/mL, control 16.4 ± 3.2 pg/mL; P < 0.05).

**Quantification of ERs in the Rat Aorta**

As shown in Figure 4, quantification of ERs in the arterial segments revealed no gender-specific differences in ER distribution between female and male rats (for either endothelial or vascular smooth muscle cells). In both genders, significantly more endothelial cells are positive for ERs than are vascular smooth muscle cells.

**Discussion**

In our experiments, short-term administration of the natural estrogen 17β-E caused a dose-dependent vasodilation with a consecutive increase in the cardiac output and ejection fraction. These results are in accordance with in vitro28,29 and
in vivo\textsuperscript{9,30} studies that describe estrogen-induced vasodilation. In vitro studies\textsuperscript{31,32} reported a more pronounced vasodilative effect in females than in males, and our results confirm this gender-specific reduction in the afterload in vivo. A clinical study in male-to-female transsexuals demonstrated that long-term estrogen therapy improved vascular function in these patients.\textsuperscript{33} Nevertheless, these results are different than the observations of Collins et al.,\textsuperscript{12} who described a modulation of the acetylcholine-induced vascular response by estrogen in the atherosclerotic coronary arteries of women but not of men. The gender-specific effects cannot be accounted for by different 17β-E plasma levels because identical 17β-E doses cause comparable plasma levels in the 2 genders. The estrogen-induced vasodilation starts in the first minute of infusion. Such a rapid onset cannot be explained by "genomic effects" that cause gene transcription and protein synthesis, which require several hours.\textsuperscript{34} Thus, the acute vascular effects of 17β-E must be "nongenomic effects." Endothelial cells\textsuperscript{35,36} and vascular smooth muscle cells\textsuperscript{23,37} express ERs. There is some evidence that acute nongenomic effects of estrogen could be mediated by receptors on the cell membrane: Wyckoff et al.\textsuperscript{38} described ERs on the plasma membrane of ovine fetal pulmonary artery endothelial cells.

In the present study, the pure estrogen antagonist ICI 182,780\textsuperscript{25} reduced the acute vascular effects of 17β-E even in male rats. However, the estrogen-induced effects were not completely prevented by ICI 182,780. Because ICI 182,780 is a competitive ER inhibitor,\textsuperscript{25} it seems possible that the administered dose was not high enough to completely prevent the effects of the pharmacological dose of 200 ng/kg 17β-E. Nevertheless, our experiments demonstrate that acute vascular effects of 17β-E are mediated in both genders, at least in part by receptors that can be blocked by ICI 182,780. Because ICI 182,780 is not a selective ER antagonist, these experiments cannot determine which receptor subtype (ER\textsubscript{α} or ER\textsubscript{β}) mediated the acute vascular effects of 17β-E in the present study. In vitro studies\textsuperscript{38} demonstrated that ICI 182,780 blocks effects of estradiol that are mediated by ER\textsubscript{α} on the plasma membrane of endothelial cells. On the other hand, 17β-E inhibits the vascular injury response in ER\textsubscript{α}-deficient mice.\textsuperscript{39} The question of which receptor subtype mediated the acute vascular effects of 17β-E in the present study cannot be answered sufficiently until highly selective ER inhibitors are available. Perhaps experiments with a predominant ER\textsubscript{β} agonist such as genistein, with binding affinity to ER\textsubscript{α} and ER\textsubscript{β} of 4% and 84%, respectively,\textsuperscript{40} will help to answer this question. Such experiments should be conducted in the future. From our experiments, we cannot conclude whether these receptors are "classic" ERs or ERs on the plasma membrane. It seems possible that the gender-specific response to 17β-E could be explained by gender-specific differences in the ER distribution, the ER density, or the ER activity. The immunohistochemical staining of the aortic vessel wall showed a characteristic ER distribution between endothelial and vascular smooth muscle cells. Our immunohistochemical study of the aortic wall showed that ERs are mainly located in the cell nucleus. Although our study excluded gender-specific differences of the ER distribution of the aortic wall, this staining provided no information regarding ER density or activity. Furthermore, there is no proof that the marked ERs are the receptors that mediated the acute effects of 17β-E in our experiments. This may also support the hypothesis that ERs on the plasma membrane mediate the acute effects of 17β-E.

There is some evidence that NO is involved in the acute estrogen-induced vasodilation. Hayashi et al.\textsuperscript{15} reported that the basal release of NO from aortic rings is enhanced in female compared with male or ovariectomized female rabbits. Kauser and Rubanyi\textsuperscript{31} observed a higher release of endothelium-derived NO from the aorta of female rats than of male rats. Physiological levels of estrogen release NO from endothelial cells of rat coronary arteries.\textsuperscript{17} Van Buren et al.\textsuperscript{41}
reported that N\textsuperscript{\textcircled{O}}-monomethyl-L-arginine (L-NMMA) antagonizes the estrogen-induced vasodilation of uterine arteries from oophorectomized ewes. In contrast, Jiang et al\textsuperscript{19} reported no effect of L-NMMA on 17β-E-induced relaxation of rabbit coronary arteries. Lamping and Nuno\textsuperscript{42} also could not detect an effect of N\textsuperscript{\textcircled{O}}-nitro-L-arginine (L-NNA) alone on the relaxation induced by 17β-E of isolated coronary microvessels from female or male dogs. Rubanyi et al\textsuperscript{34} showed that ERs play a role in the regulation of endothelial NO production, and Wyckoff et al\textsuperscript{38} described acute activation of endothelial NO synthase by estradiol in endothelial cells of ovine fetal pulmonary arteries mediated by ERα on plasma membranes that can be blocked by ICI 182,780. Our in vivo experiments using the nonselective NO synthase inhibitor L-NAME\textsuperscript{39} show that the acute estrogen-induced vasodilation is completely abolished after pretreatment with L-NAME. This prevention of the estrogen-induced vasodilation cannot be explained by the known vasoconstrictive effect of L-NAME, because the absolute value of the calculated total peripheral resistance at the beginning of 17β-E infusion is not higher in the L-NAME groups than in the groups without L-NAME pretreatment (Table 1). Therefore, we conclude

<table>
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<tr>
<th>Parameter</th>
<th>Time</th>
<th>Control</th>
<th>17β-E</th>
<th>Control</th>
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<td>103.8±1.4</td>
<td>104.4±3.9</td>
<td>114.7±3.6</td>
<td>105.3±5.4</td>
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<td>5&lt;sub&gt;post&lt;/sub&gt;</td>
<td>99.2±1.8</td>
<td>103.5±1.4</td>
<td>109.2±3.4*</td>
<td>101.7±1.4</td>
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<tr>
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<td>15&lt;sub&gt;post&lt;/sub&gt;</td>
<td>98.7±1.8</td>
<td>103.8±1.4</td>
<td>106.4±2.8*</td>
<td>98.7±0.6</td>
</tr>
<tr>
<td>Peak LVSP</td>
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<td>98.1±1.5</td>
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<td>97.5±1.0</td>
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<td>95.3±0.8*</td>
<td>96.9±0.8</td>
<td>98.3±1.3</td>
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<td>99.1±1.4</td>
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<tr>
<td>Peak dP/dt&lt;sub&gt;max&lt;/sub&gt;</td>
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<td>99.4±5.9</td>
<td>97.9±1.5</td>
<td>98.3±2.1</td>
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<td></td>
<td>5&lt;sub&gt;post&lt;/sub&gt;</td>
<td>101.0±3.4</td>
<td>101.4±5.6</td>
<td>97.4±2.1</td>
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<td>101.4±3.1</td>
<td>98.8±6.0</td>
<td>96.6±2.4</td>
<td>98.3±3.3</td>
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LVEDP indicates left ventricular end-diastolic pressure; AoP<sub>a</sub>, mean aortic pressure; AoP<sub>di</sub>, diastolic aortic pressure; HR, heart rate; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; peak LVSP and peak dP/dt<sub>max</sub>, data derived from isovolumic maximum beat; 7<sub>inf</sub>, at termination of infusion; 5<sub>post</sub> and 15<sub>post</sub>, 5 and 15 minutes after infusion. Values are mean±SEM in percentage of preinfusion values. *P<0.05, †P<0.01, ‡P<0.001 vs control.
from our results that estrogen-induced vasodilatation is completely mediated by NO. Furthermore, 17β-E is an oxygen radical scavenger\(^1\) that increases the half-life of NO.\(^2\) The loss of endothelial NO-production contributes to the development of atherosclerosis,\(^3\) and NO improves endothelial dysfunction. Because estrogen also modulates or even abolishes endothelial dysfunction,\(^4\) this effect of estrogen may be mediated by NO. Thus, it seems possible that the NO-mediated effects of estrogen may be involved in the atheroprotective effects of estrogen.

In addition to its reduction in the blood vessels, 17β-E acutely increases cardiac output and ejection fraction, so we cannot conclude from these data in the intact circulation the acute effects of 17β-E on myocardial contractility. To study the inotropic effects of 17β-E in vivo, we performed further isovolumic measurements independent of preload and afterload conditions. These isovolumic measurements showed that 17β-E has no acute effect on myocardial contractility.

In summary, our study verifies that 17β-E in vivo is oxygen radical scavenger and increases the half-life of NO. These results are consistent with previous studies showing that estrogen increases the half-life of NO.\(^5\) The acute effects of 17β-E on myocardial contractility are consistent with previous studies showing that estrogen increases cardiac output and ejection fraction.

References


Acute Gender-Specific Hemodynamic and Inotropic Effects of 17β-Estradiol on Rats
Martin E. Beyer, Georg Yu, Hartmut Hanke and Hans Martin Hoffmeister

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