Effects of Physiological Levels of Estrogen on Coronary Vasomotor Function in Postmenopausal Women

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Background Estrogen replacement therapy has been associated with a reduction in cardiovascular events in postmenopausal women. One of the mechanisms responsible may be a beneficial effect of estrogen on coronary vascular function. We therefore studied the short-term effects of estrogen on coronary artery dimensions and microvascular resistance in postmenopausal women.

Methods and Results Twenty postmenopausal women 61±7 years old participated in this study. Seven had angiographic evidence of atherosclerosis of the left coronary artery. Coronary artery diameters were measured by quantitative coronary angiography. Blood flow velocity was measured with a Doppler wire placed in a proximal left coronary artery segment. Left coronary artery infusions of acetylcholine (range, 10^{-8} to 10^{-3} mol/L estimated delivered concentrations) and of adenosine (n=18) and sodium nitroprusside (n=10) were performed before and during concomitant continuous intracoronary infusion of 17β-estradiol to test endothelium-dependent and independent vasodilation, respectively. Intracoronary infusion of estradiol increased coronary sinus estradiol levels from postmenopausal (16±11 pg/mL) to premenopausal (282±121 pg/mL) levels. Estradiol did not affect basal coronary artery diameter, blood flow, or resistance. Epicardial coronary artery constriction induced by acetylcholine infusion in the control study (maximum, 10±15% from baseline) was prevented during repeat acetylcholine infusion with concomitant estradiol administration (P<.001). Estradiol potentiated the vasodilator coronary microvascular response to acetylcholine as manifest by significantly greater coronary flow (P<.001) and lower coronary resistance (P<.02). The reduction in coronary resistance from baseline in response to acetylcholine was significantly potentiated by estradiol (P=.01), with a mean decrease in coronary vascular resistance during acetylcholine infusion of 20±38% before and 35±33% during concomitant estradiol administration. The effect of estradiol on coronary dynamics was similar in women with and without angiographically apparent left coronary artery atherosclerosis and was most prominent in women with the most impaired responses to acetylcholine at both the epicardial (r=-.72, P<.001) and microvascular (r=-.59, P=.006) coronary artery levels. In contrast, estradiol did not affect the coronary epicardial or microvascular vasodilator responses to adenosine or sodium nitroprusside.

Conclusions Physiological levels of 17β-estradiol acutely and selectively potentiate endothelium-dependent vasodilation in both large coronary conductance arteries and coronary microvascular resistance arteries of postmenopausal women. This effect may contribute to the reduction in cardiovascular events observed with estrogen replacement therapy. (Circulation. 1994;89:2545-2551.)

Key Words • estrogen • menopause • coronary artery disease • endothelium • nitric oxide

A number of studies have examined the prevalence of coronary artery disease in postmenopausal women according to the use of hormone replacement therapy.1,2 These studies have consistently shown a lower prevalence of atherosclerosis and significant coronary disease in women receiving hormone replacement therapy. A number of epidemiological studies, the largest of which was the Nurses’ Health Study,3 have shown that the use of hormone replacement therapy is associated with a decreased incidence of cardiovascular events, even when other risk factors for atherosclerosis are taken into account.1,2 One of the main beneficial actions of estrogen may be to decrease low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL) cholesterol.4,5 However, these lipid changes have been calculated to be insufficient to explain the almost 50% reduction in events observed with treatment.1 Thus, additional mechanisms of estrogen benefit must be considered.

Animal studies have suggested a variety of vascular effects of estrogen. Gisclard et al6 reported enhanced relaxation of femoral artery rings from estrogen-treated ovariectomized rabbits in response to acetylcholine compared with untreated animals. Williams et al7,8 reported that short-term or long-term administration of estrogen prevented constriction of atherosclerotic epicardial coronary arteries in response to the endothelium-dependent vasodilator acetylcholine in ovariectomized cynomolgus monkeys fed an atherogenic diet. Other in vitro studies have suggested that estradiol augments endothelium-dependent contraction to arachidonic acid9 and that estrogen is an endothelium-independent vasodilator at supraphysiological concentrations.10 Reis et al11 recently reported that intravenous ethinyl estradiol increased basal coronary flow and epicardial coronary artery diameter in postmenopausal women and prevented acetylcholine-induced decreases in coronary artery diameter and flow in a subset of patients. However, this dose of estrogen likely achieved
supraphysiological levels, and no study was performed to determine whether these estrogen effects were endo-
thelium dependent. We undertook the present study to examine the short-term effects of estrogen at physiologi-
cal concentrations on basal coronary artery dimensions and microvascular resistance and on the vasodilator responses of the coronary circulation to both endo-
thelium-dependent and endothelium-independent agonists in estrogen-deficient postmenopausal women.

Methods

Study Population

All women were less than 75 years old, had not had a menstrual period for at least 6 months, and had not received any hormone replacement treatment within the preceding 6 months. Serum estradiol levels were required to be <50 pg/mL. Patients were studied at the time of diagnostic cardiac catheterization, which was performed for evaluation of cardiac symptoms and/or abnormal noninvasive test results suggestive of ischemic heart disease. They were excluded from study if they had unstable angina, cardiac failure, severe hypertension off medication, untreated hypothyroidism, or any other major systemic illness before catheterization or if they were found to have severe left coronary artery disease (>70% stenosis) at catheterization precluding safe intracoronary administration of relatively high concentrations of acetylcholine. Twenty-one postmenopausal women participated in the study. One was subsequently excluded because of technically unreliable Doppler flow velocity measurements; thus, 20 women composed the final study group (mean age, 61±7 years; range, 49 to 73 years). Of these 20 women, 15 (75%) had a history of hypertension, 6 (30%) had a total cholesterol level >250 mg/dL, and 4 (20%) had diabetes mellitus. Seventeen women (85%) had one or more of these risk factors for atheroscler-
osi. At coronary angiography, 7 patients were found to have evidence of atherosclerosis of the left coronary artery (2 patients with >50% stenoses), 2 patients had right coronary artery disease only (both <50% stenoses), and 11 patients had angiographically smooth coronary arteries. The study was approved by the National Heart, Lung, and Blood Institute Review Board, and all study participants gave written in-
formed consent.

Protocol

All medications, except for diabetic medication (4 patients) and thyroid replacement therapy (4 patients), were stopped at least five drug half-lives before study. Aspirin and nonsteroidal antiinflammatory drugs were stopped at least 10 days before study. Cardiac catheterizations were performed after an over-
night fast, with 10 mg diazepam PO given as premedication. Additional diazepam (2 to 3 mg) was given as needed to maintain patient comfort during the study, which lasted approximately 1.5 hours after diagnostic angiography. After diagnostic right- and left-side catheterization and angiography with 10,000 U heparin IV for anticoagulation, a 6F Judkins catheter was advanced to the ostium of the left coronary artery. A 0.018-in. 12-MHz Doppler wire (Cardiometrics Inc)13 was advanced through this catheter into the proximal left coronary artery that was either angiographically smooth or, if atherosclerotic, without stenosis >50% luminal narrow-
ing. The wire tip was positioned such that a characteristic and stable flow velocity waveform was obtained. In 1 woman, the wire tip was placed in the left main artery; in 14 women, in the left anterior descending coronary artery; and in 5 women, in the circumflex coronary arteries. On-line measurements were made of average peak flow velocity. Each value was taken as the average of three cardiac cycles. In 18 women, a 6F multipurpose catheter was introduced via the right internal jugular vein into the great cardiac vein and was used to sample blood for estradiol levels with comparison to femoral artery levels. Estradiol concentrations were subsequently measured by radioimmunoassay (Diagnostic Products Corp).

Agonist Infusions

To assess endothelium-dependent vasodilator responses, we infused acetylcholine (dissolved in 5% dextrose) into the left main coronary artery for 2 minutes at a rate of 1 mL/min before blood flow measurements were performed. Acetylcho-
line was administered in the following estimated intracoronary concentrations (in mol/L): 10⁻⁶ (0.29 μg/min), 10⁻⁷ (2.9 μg/ min), 10⁻⁸ (29 μg/min), 3.3 x 10⁻⁹ (96 μg/min), and 10⁻¹⁰ (290 μg/min), with each dose administered for 2 minutes. Incre-
mental doses of acetylcholine were given until a dose was reached that decreased the coronary flow velocity response (designated Ach 2) compared with the flow velocity obtained with the prior lower concentration of acetylcholine (designat-
ed Ach 1). These two doses of acetylcholine were subsequently repeated during the estradiol study. At the end of each infusion, coronary flow velocity and mean blood pressure were recorded, and a coronary angiogram was performed.

To assess endothelium-independent vasodilator responses, adenosine (dissolved in 5% dextrose at a final concentration of 2.2 mg/mL) was infused into the left main coronary artery for 2 minutes at a rate of 1 mL/min in 18 patients, and sodium nitroprusside was infused at a concentration of 40 μg/mL into the left main coronary artery for 3 minutes at a rate of 1 mL/min in 10 patients. At the end of each infusion, flow velocity and mean blood pressure were recorded, and a coronary angiogram was performed.

Control Study

In the first 10 patients of this study, 5% dextrose was infused into the left main coronary artery at a rate of 1 mL/min continuously while baseline measurements of flow velocity and angiography were obtained, followed by measurement of the responses to the acetylcholine, nitroprusside, and adenosine. To achieve solubility in 5% dextrose, 17β-estradiol (United States Pharmacopeia) required dilution in ethanol. The estra-
diol concentration of 75 ng/mL used in this study contained 2.5% ethanol. To determine if ethanol alone in this concen-
tration could affect coronary vasomotion, we infused a 2.5% solution of ethanol (1 mL/min) into the left coronary artery, replacing the 5% dextrose infusion. After repeat baseline measurements, the concentration of acetylcholine that achieved the highest coronary flow velocity during dextrose infusion was repeated in 17 women; adenosine infusion was repeated in 4 women. The data of the first 10 women tested in this way demonstrated no effect of ethanol diluent alone on the responses to these agonists compared with 5% dextrose. Thus, in the remaining 10 women studied, the control vasodi-
lator responses to acetylcholine, adenosine, and sodium nitro-
prusside were obtained only during ethanol diluent infusion.

Estradiol Study

A 10-minute rest period was allowed after completion of the control study. An intracoronary infusion of 17β-estradiol (75 ng/mL) was then begun at a rate of 1 mL/min. The aim of the infusion was to increase coronary estradiol levels to approxi-
mately 300 pg/mL, typical midcycle premenopausal values.15 Fifteen minutes after the estradiol infusion began, baseline measurements were repeated, and the two highest concentra-
tions of acetylcholine that had been administered during the control study (Ach 1 and Ach 2) were repeated. Adenosine (n=18) and sodium nitroprusside (n=10) infusions were also repeated during continuation of the estradiol infusion.

Quantitative Coronary Angiography and Computation of Volume Flow

Left coronary angiograms were obtained in a right anterior oblique projection for measurement of epicardial coronary diameter at baseline and after each drug infusion, using hand
injections of approximately 6 mL ioxaglate (Hexabrix, Mallinckrodt Medical). Coronary artery diameter changes were measured with a computerized edge-detection system with ARTREK software (Quantum 2000 I, Stat View, Image-Comm Systems, Inc.) by a technician who was not involved in the performance of the study and had no knowledge of the coronary flow velocity data. Coronary diameter was measured at 0.5 cm beyond the tip of the Doppler wire. A quantitative estimate of coronary blood flow was calculated from the Doppler flow velocity and quantitative angiographic data using the following equation:

\[ Q = \pi D^2/4(\text{APV}/2)(0.6) \]

where \( Q \) is flow (mL/min), \( D \) is vessel diameter (mm), and \( \text{APV} \) is average peak velocity (cm/s). \(^{21}\) In the 7 women with left coronary artery atherosclerosis, additional quantitative angiographic measurements were made at the lesion site.

**Statistical Analysis**

Student’s \( t \) test for paired data was used to compare baseline measurements and the responses to sodium nitroprusside and adenosine before and after interventions. The dose-response curves to acetylcholine obtained before and after estradiol were compared by repeated-measures ANOVA, allowing for interaction. Associations between the effects of estradiol and demographic, laboratory, and hemodynamic parameters were assessed by performing linear regression analysis and calculation of a correlation coefficient. Data are expressed as mean±1 SD. Error bars on the figures represent ±1 SEM.

**Results**

**Vascular Effect of Ethanol Diluent**

The replacement of an intracoronary infusion of 5% dextrose with 2.5% ethanol did not significantly affect resting coronary blood flow (50±28 to 46±25 mL/min) or resistance (3.2±1.8 to 3.3±2.0 mm Hg/mL per minute). Furthermore, the coronary flow (66±42 to 74±57 mL/min) and resistance (2.4±1.2 to 2.6±1.7 mm Hg/mL per minute) responses to acetylcholine (median delivered concentration, 10\(^{-6}\) mol/L) were unchanged by 2.5% ethanol compared with the preceding 5% dextrose infusion. The coronary flow (232±116 to 229±109 mL/min) and resistance (0.63±0.26 to 0.64±0.29 mm Hg/mL per minute) responses to adenosine were likewise unaltered by 2.5% ethanol compared with 5% dextrose.

**Vascular Effect of Estradiol**

Intracoronary infusion of estradiol increased coronary sinus estradiol levels from postmenopausal (16±11 pg/mL) to premenopausal (282±121 pg/mL) levels. Estradiol had no significant effect on baseline epicardial coronary artery diameter (2.7±0.7 to 2.8±0.7 mm), coronary blood flow (45±23 to 50±28 mL/min), or vascular resistance (3.4±1.9 to 3.1±1.6 mm Hg/mL per minute) compared with the preceding control study baseline measurements.

During the control study, the two highest concentrations of acetylcholine used (which included the dose producing the highest coronary flow velocity, Ach 1) were designated Ach 1 (median delivered concentration, 10\(^{-6}\) mol/L) and Ach 2 (median delivered concentration, 3.3×10\(^{-6}\) mol/L) (Table). Epicardial coronary artery constriction induced by Ach 1 and Ach 2 (maximum, 10±15% from baseline) in the control study was prevented during repeated doses of Ach 1 and Ach 2 with concomitant estradiol infusion (\( P<.001 \)) (Fig 1).

Estradiol potentiated the coronary microvascular vasodilator responses to Ach 1 and Ach 2 compared with the control study, as manifest both by increased coronary blood flow (\( P<.001 \)) and reduced coronary resistance (\( P=.02 \)) (Fig 2). The reduction in coronary resistance from baseline in response to acetylcholine was significantly potentiated by estradiol (\( P=.01 \)), with the mean decrease in coronary vascular resistance from baseline in response to Ach 1 and Ach 2 20±38% before and 35±33% after estradiol. In contrast, estradiol did not affect the coronary artery diameter responses or the coronary flow and resistance responses to adenosine or to sodium nitroprusside (Fig 3). The decrease in coronary vascular resistance from baseline with adenosine was 74±8% before and 74±6% after estradiol, and the decrease in resistance from baseline with sodium nitroprusside was 53±24% before and 59±8% after estradiol.

In the 7 women with angiographic evidence of atherosclerosis in the left coronary artery, Ach 2 resulted in a change in diameter at the site of plaque formation from 2.0±0.8 mm at baseline to 1.9±0.7 mm during the control study and from 1.9±0.8 mm at baseline to 2.0±0.8 mm during estradiol infusion. The magnitude of this effect of estradiol was similar in the 13 women with angiographically smooth coronary arteries; in response to Ach 2, proximal segment diameters at the Doppler wire tip changed from 2.7±0.7 mm at baseline to 2.4±0.8 mm during the control study and from 2.7±0.5 to 2.6±0.6 mm during estradiol infusion. The effect of estradiol on the mean decrease in coronary vascular resistance from baseline in response to Ach 1 and Ach 2 was similar for the women with left coronary artery atherosclerosis (−35±31% to −46±16%) and the women with smooth left coronary arteries (−13±40% to −30±39%).

Because estradiol blocked the epicardial coronary artery constriction produced by acetylcholine, correlations were sought between the magnitude of this effect and several demographic, laboratory, and hemodynamic parameters. Patients with the greatest epicardial coronary artery constrictor response to the acetylcholine during the control study (median concentration, 3.3×10\(^{-6}\) mol/L) had the greatest dilator response to the same dose of acetylcholine following estradiol administration (\( r=−.72, P<.001 \)). However, this estradiol effect did not correlate with the postinfusion estradiol level (\( r=−.34 \)), age (\( r=−.33 \)), total cholesterol (\( r=−.07 \)), HDL cholesterol (\( r=−.02 \)), LDL cholesterol (\( r=−.02 \)), or mean arterial pressure (\( r=−.44 \)). Because estradiol augmented the fall in coronary resistance produced by acetylcholine, correlations were sought between the magnitude of this effect and these same parameters. Patients with the least vasodilatation in response to acetylcholine (median concentration, 10\(^{-6}\) mol/L) during the control study had the greatest vasodilator response to the same dose of acetylcholine after estradiol administration (\( r=−.59, P=.0058 \)). This estradiol effect did not correlate with the postinfusion estradiol level (\( r=−.24 \)), age (\( r=−.01 \)), total cholesterol (\( r=−.09 \)), HDL cholesterol (\( r=−.12 \)), LDL cholesterol (\( r=−.18 \)), or mean arterial pressure (\( r=.08 \)).

**Discussion**

The present study shows that acute intracoronary administration of estradiol to postmenopausal women,
Acetylcholine Concentrations That Produced Highest Coronary Flow Velocity (Ach 1) and Next Higher Acetylcholine Concentration Resulting in Relative Constriction (Ach 2), Administered During Control and Estradiol Studies

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Ach indicates acetylcholine. 10^-7 mol/L=2.9 µg/mL, 10^-6 mol/L=29 µg/mL, 3.3x10^-6 mol/L=96 µg/mL, 10^-5 mol/L=290 µg/mL. *P<.001 vs Ach 2 control flow.

which achieves physiological levels of this hormone in the heart, improves responses of the coronary circulation to the endothelium-dependent vasodilator acetylcholine. At the large-vessel level, the vasoconstriction produced by acetylcholine in both angiographically smooth and atherosclerotic segments was prevented by estradiol. Those women who before estradiol administration had the greatest constrictor response to acetylcholine demonstrated the greatest vasodilator response to the same dose of acetylcholine with concomitant estradiol infusion. We also found that estradiol augmented the fall in coronary resistance induced by acetylcholine, a change associated with a significant increase in coronary blood flow. Because the epicardial left coronary arteries were free of angiographically significant disease in all except 2 patients and because the effect of estradiol on epicardial coronary artery diameters was small, our study indicates that an effect of estradiol also occurred at the level of small intramyocardial resistance vessels during acetylcholine administration. The women who before estradiol administration exhibited the most impaired microvascular vasodilator response to acetylcholine demonstrated the greatest increase in coronary flow during repeated administration of the same dose of acetylcholine with concomitant estradiol infusion. Importantly, the effects of estradiol on epicardial arteries and the microcirculation were noted at physiological levels of the hormone.13 Reports from other groups have suggested beneficial effects of estrogen on coronary artery hemodynamics of postmenopausal women.11,14-17 In none of these studies were...
plasma levels of estrogen (before and after infusion) reported. This issue is important because supraphysiological concentrations of estrogen may have direct

smooth muscle-relaxant effects. Such an effect of acutely administered sublingual 17β-estradiol, achieving supraphysiological plasma levels, might have accounted for the improvement in exercise tolerance in women with coronary artery disease recently reported by Rosano et al.17

Our observations support the findings of in vitro and in vivo animal studies that showed beneficial effects of estrogen administration on coronary vascular responses to acetylcholine. Williams et al demonstrated a coronary vasoconstrictor response to acetylcholine in estrogen-deficient cynomolgus monkeys fed an atherogenic diet. In their initial study, randomization of monkeys to 2 years of estrogen replacement resulted in coronary vasodilator responses to acetylcholine compared with vasoconstriction noted in untreated monkeys. Histological examination showed that the degree of intimal thickening was less in the coronary arteries from estrogen-treated monkeys, and this was associated with lower plasma total cholesterol and higher HDL cholesterol levels than found in untreated monkeys. Thus, the improvement in acetylcholine responses in estrogen-treated animals might have resulted from a reduced burden of atherosclerosis in the vessel wall. In their second study, however, using the same animal model, acute intravenous administration of estradiol changed the acetylcholine response from vasoconstrictor response to either no change in diameter or dilation. In neither study was there any difference in the response to nitroglycerin in treated versus untreated animals. These studies only measured epicardial coronary artery diameter and did not assess the impact of estradiol administration on coronary blood flow or on the coronary microcirculation.

The prevention of acetylcholine-induced constriction of epicardial coronary arteries by estradiol may be due to interference with muscarinic receptor activation on smooth muscle as opposed to enhancement of release of vasodilating substances from the endothelium. However, acetylcholine produced a fall in coronary vascular resistance and an increase in coronary blood flow compared with baseline measurements. Augmentation of this microvascular vasodilator response to acetylcholine by estradiol, in the absence of any effect of estradiol on endothelium-dependent vasodilation at the large- or small-artery level, suggests that the vascular effect of estradiol is mediated through potentiation of an endothelium-dependent vasodilating mechanism. Furthermore, in a previous study, we found that estradiol acutely potentiates acetylcholine-induced vasodilation in the forearm, a vascular bed that does not vasoconstrict in response to acetylcholine at the concentrations used in obtaining dose-response curves in our laboratory. The vasodilator effect of estradiol on epicardial arteries could be a consequence of the increased basal and acetylcholine-stimulated coronary flow, with increased epicardial shear stress, as opposed to a direct effect on the epicardial endothelium. However, the likelihood of a direct effect of estradiol on the endothelium of epicardial arteries is supported by the in vitro studies of Gisclard et al, in which enhancement of acetylcholine-induced relaxation of femoral artery rings with intact endothelium was noted in vessels from estradiol-treated animals compared with untreated animals.

Fig 2. Plots of coronary flow (top) and resistance (bottom) at baseline and in response to that dose of acetylcholine that produced the highest flow during the control study (Ach 1 median concentration, 10^-6 mol/L) and the next higher concentration of acetylcholine that resulted in a lesser increase in flow (Ach 2 median concentration, 3.3×10^-6 mol/L) with measurements made during the control study compared with repeat measurements at the same doses of acetylcholine during intracoronary infusion of 75 ng/mL estradiol. Data are expressed as mean±SEM.

Fig 3. Bar graphs of coronary artery diameter of a left coronary artery segment measured 0.5 cm distal to the tip of the flow velocity wire (top), coronary flow (middle), and coronary resistance (bottom) during infusions of 40 μg/min sodium nitroprusside and 2.2 ng/min adenosine during the control study compared with repeat measurements at the same doses of these agonists during intracoronary infusion of 75 ng/mL estradiol. Data are expressed as mean±SEM.
The findings of the present study are compatible with estradiol-mediated enhancement of the release of relaxant factors from the endothelium. We tested the effect of estradiol on two doses of acetylcholine: the dose that produced the greatest magnitude of microvascular vasodilation and the next higher dose that produced relative vasoconstriction, thus overwhelming the effect of endothelial release of relaxant factors by direct smooth muscle muscarinic effects. The vasodilator responses to both doses of acetylcholine were augmented by estradiol. The immediacy of the effect suggests that activation of gene transcription and protein synthesis is not the mechanism. Potentiation of agonist-stimulated flow could be a result of the effects of estrogen at the endothelial cell surface receptor level or at the level of production of the known endothelin-derived relaxing factors nitric oxide, prostacyclin, and endothelin-derived hyperpolarizing factor.21,22 In addition, estrogen is known to have antioxidant properties,23 which could facilitate nitric oxide production or prolong its half-life, with beneficial effects on endothelial signal-transduction pathways that link cell surface receptor activation and nitric oxide production.24

The release of vasodilating substances by the endothelium is reduced in coronary artery disease and in conditions associated with an increased risk of atherosclerosis, such as hypertension, hypercholesterolemia, and diabetes.25-32 Indeed, the majority of women in our study (85%) had one or more of these risk factors for atherosclerosis and vascular dysfunction. Enhancement of production of endothelin-derived vasodilating substances by estrogen could lead to improvement in coronary flow reserve or coronary hemodynamic responses to stress. Additional estrogen benefit to the endothelium is possible. For example, in addition to controlling vascular tone, normal endothelium has antplatelet, anti-thrombotic, and fibrinolytic actions.22,33,34 Thus, intact functioning endothelium may not only prevent vasoconstriction but also prevent thrombosis in the coronary circulation. Because acute cardiovascular events commonly relate to coronary vasoconstriction and thrombosis, it is an attractive hypothesis to suggest that the beneficial effect of estrogen on the coronary endothelium demonstrated in the present study is one of the mechanisms of the long-term benefit of estrogen replacement treatment with regard to cardiovascular morbidity and mortality in postmenopausal women.

It is noteworthy that the coronary sinus estradiol levels achieved in the present study were typical of premenopausal values. It remains to be determined whether the same vascular effects would be observed at a lower dose of estrogen than used in our study or with estrogens other than 17β-estradiol. It is also unknown whether the effect demonstrated with short-term replacement will be observed with long-term therapy, although the animal data suggest that it would be. Further studies are needed to determine whether long-term estrogen replacement has any direct anti-ischemic benefit as a consequence of favorable effects on coronary endothelial function.

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Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women.
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