Effect of Estrogen Replacement Therapy on Endothelial Function in Peripheral Resistance Arteries in Normotensive and Hypertensive Postmenopausal Women

Yukihito Higashi, Mitsuhiro Sanada, Shota Sasaki, Keigo Nakagawa, Chikara Goto, Hideo Matsuura, Koso Ohama, Kazuaki Chayama, Tetsuya Oshima

Abstract—Both menopause and hypertension are associated with endothelial dysfunction and are risk factors for coronary heart disease. We evaluated forearm resistance artery endothelial function in hypertensive postmenopausal women (HPW, n=57) and compared it with endothelial function in normotensive postmenopausal women (NPW, n=67). In addition, we evaluated the effects of long-term estrogen replacement therapy (ERT, conjugated equine estrogen at a dose of 0.625 mg daily for 12 weeks) on endothelial function in HPW (n=10) and NPW (n=35). Forearm blood flow (FBF) was measured by strain-gauge plethysmography during reactive hyperemia to assess endothelium-dependent vasodilation and after sublingual nitroglycerin (NTG) administration to assess endothelium-independent vasodilation. Basal FBF was similar in the NPW and HPW groups. The FBF in the HPW group during reactive hyperemia was significantly lower than that in the NPW group. Increases in FBF after NTG were similar in the 2 groups. ERT decreased the LDL cholesterol concentration and circulating ACE activity and increased estradiol and HDL cholesterol in both groups. Basal blood pressures, heart rate, FBF, and body weight did not change with ERT. After 12 weeks of ERT, the maximal FBF response during reactive hyperemia increased significantly in both groups. The improvement in reactive hyperemia after ERT was significantly greater in the HPW group than in the NPW group (49±6% versus 17±5%, P<0.05). Changes in FBF after sublingual NTG administration were similar before and after 12 weeks of ERT. These findings suggest that continued ERT improves forearm resistance artery endothelial function in postmenopausal women and that this beneficial effect is greater in patients that are hypertensive. (Hypertension. 2001;37[part 2]:651-657.)

Key Words: estrogen ■ women ■ hypertension, essential ■ endothelium ■ nitroglycerin

Recent epidemiological studies have shown that estrogen replacement therapy (ERT) reduces cardiovascular morbidity and mortality rates in postmenopausal women, although a well-controlled clinical trial Heart and Estrogen/Progestin Replacement Study failed to show a reduction in coronary heart disease (CHD) in postmenopausal women receiving ERT combined with progestin. ERT in postmenopausal women is also associated with beneficial changes in the lipid profile. However, the lipid-lowering effects of ERT reduce cardiovascular events by ≈25% to 50% in postmenopausal women, suggesting that non–lipid-related mechanisms contribute to the cardioprotective effects of ERT. Recently, it has been reported that ERT augments endothelium-dependent vasodilation of the brachial and coronary arteries in postmenopausal women. These findings suggest that enhanced nitric oxide (NO) production may, at least in part, participate in the cardioprotective effects of ERT by inhibiting the aggregation and adhesion of platelets, preventing leukocyte adhesion to the vascular wall, and suppressing smooth muscle cell proliferation.

Hypertension also increases the incidence of CHD. Several studies have demonstrated endothelial dysfunction in patients with essential hypertension. Impaired endothelial function predicts the development of atherosclerosis in both animals and humans. It has been postulated that endothelial dysfunction may contribute to menopause- and hypertension-induced CHD. However, there is little information regarding the interdependent and independent effects of menopause and hypertension on endothelial function. Whether endothelial function is restored by ERT in postmenopausal women with hypertension is, therefore, an important issue. The purpose of this study was to determine whether endothelial dysfunction is demonstrable in the forearm microvascular circulation of hypertensive postmenopausal women (HPW) compared with...
normotensive postmenopausal women (NPW) and whether the effects of long-term ERT on forearm resistance artery endothelial function are different between NPW and HPW. We measured the response of forearm blood flow (FBF) to reactive hyperemia, an index of endothelium-dependent vasodilation, and to nitroglycerin (NTG), an index of endothelium-independent vasodilation.

Methods

Study Protocol 1: Forearm Resistance Artery Endothelial Function in NPW and HPW

We studied 69 Japanese NPW (mean age, 52±5 years; range, 47 to 58 years) and 57 HPW (mean age, 53±4 years; range, 47 to 57 years). Each patient had natural menopause for 1 to 5 years previously. Menopausal status was confirmed by a serum follicle-stimulating hormone (FSH) concentration >40 mIU/mL and a serum estradiol concentration <73 pmol/L (20 pg/mL). Before entering the study, each patient underwent a physical examination including a gynecological evaluation and mammography. Hypertension was defined as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg measured in a sitting position on at least 3 different occasions in the outpatient clinic of Hiroshima University School of Medicine. Patients with secondary forms of hypertension were excluded on the basis of a complete history and physical examination, radiological and ultrasound examinations, and urinalysis. Plasma renin activity (PRA) and plasma aldosterone and norepinephrine concentrations and serum creatinine, potassium, electrolytes. The serum concentration of LDL was determined with routine analytical methods used to determine serum concentrations of total cholesterol, HDL cholesterol, triglycerides, creatinine, glucose, and electrolytes. The serum concentration of LDL was determined with Friedewald's method. Serum concentrations of FSH and estradiol were measured by radioimmunoassay. Serum ACE activity was measured by a colorimetric method. PRA was assayed by radioimmunoassay. The plasma concentration of norepinephrine was measured by a colorimetric method. PRA was assayed by radioimmunoassay. The plasma concentration of norepinephrine was measured by a colorimetric method. PRA was assayed by radioimmunoassay. The plasma concentration of norepinephrine was measured by a colorimetric method. PRA was assayed by radioimmunoassay.

Statistical Analysis

Results are presented as mean±SD. Values of \( P<0.05 \) were considered significant. The Mann-Whitney U test was used to evaluate differences for baseline parameters between NPW and HPW. Comparisons of parameters before and after ERT were performed for adjusted means by ANCOVA, with the baseline data used as covariates. Comparisons of time-course curves of parameters during reactive hyperemia were analyzed by 2-way ANOVA for repeated measures. The data were processed with the software packages StatView IV (Brainpower) or Super ANOVA (Abacus Concepts).

Study Protocol 2: Effect of ERT on Forearm Resistance Artery Endothelial Function in NPW and HPW

Thirty-five among 69 NPW (mean age, 52±4 years; range, 47 to 57 years) and 10 among 57 HPW (mean age, 51±3 years; range, 46 to 56 years) who were diagnosed mild hypertension (stage I) based on the guidelines of the sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) received conjugated equine estrogen (Asahi Chemicals Co) at a dose of 0.625 mg daily each morning for 12 weeks. A 4-week run-in period was followed by a 12-week treatment period. Ten of the 69 NPW (mean age, 53±4 years; range, 47 to 56 years) and 8 of the 57 HPW (mean age, 52±3 years; range, 48 to 56 years) with mild hypertension continued 12 weeks of follow-up, not taking ERT. None of the subject had received or was taking antihypertensive therapy before and during the study.

Blood pressures were stable at the beginning of protocol 2. The vasodilatory responses to reactive hyperemia and sublingual NTG were evaluated by a protocol identical to that used in study protocol 1 at the beginning and end of the 12-week follow-up period. We confirmed the reproducibility of reactive hyperemia and sublingual NTG-induced vasodilation twice at the beginning and end of the 12-week follow-up period in 10 healthy male subjects (mean age, 27±4 years). The coefficients of variation were 4.2% and 2.4%, respectively.

Analytical Methods

Samples of venous blood were placed in polystyrene tubes containing sodium EDTA (1 mg/mL). The EDTA-containing tubes were chilled promptly in an ice bath, and the plasma was separated by centrifugation at 3100g and 4°C for 10 minutes. Serum was separated by centrifugation at 1000g at room temperature for 10 minutes. Samples were stored at −80°C until assayed. Routine analytical methods were used to determine serum concentrations of total cholesterol, HDL cholesterol, triglycerides, creatinine, glucose, and electrolytes. The serum concentration of LDL was determined with Friedewald’s method. Serum concentrations of FSH and estradiol were measured by radioimmunoassay. Serum ACE activity was measured by a colorimetric method. PRA was assayed by radioimmunoassay. The plasma concentration of norepinephrine was measured by high-performance liquid chromatography.

Results

Study Protocol 1: Effects of Reactive Hyperemia and Sublingual NTG on FBF in NPW and HPW

The baseline clinical characteristics of the NPW and HPW groups are summarized in Table 1. The systolic and diastolic
TABLE 1. Clinical Characteristics of Postmenopausal Normotensive and Hypertensive Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n=69)</th>
<th>Hypertensive (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.6±2.8</td>
<td>22.7±3.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114.3±8.2</td>
<td>153.6±15.4*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67.7±6.3</td>
<td>96.2±9.7*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68.2±6.2</td>
<td>70.2±6.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.67±1.02</td>
<td>3.91±1.17</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.74±0.32</td>
<td>1.67±0.36</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>4.8±0.6</td>
<td>5.1±0.7</td>
</tr>
<tr>
<td>Serum glucose, mmol/dL</td>
<td>55.8±10.8</td>
<td>62.1±12.5</td>
</tr>
<tr>
<td>Plasma norepinephrine, pmol/L</td>
<td>1.19±0.88</td>
<td>1.56±1.02</td>
</tr>
<tr>
<td>PRA, ng/mL per hour</td>
<td>1.16±0.51</td>
<td>1.28±0.72</td>
</tr>
<tr>
<td>Serum ACE activity, IU/L</td>
<td>13.1±3.5</td>
<td>13.2±3.4</td>
</tr>
<tr>
<td>Estradiol, pmol/L</td>
<td>61±18</td>
<td>59±15</td>
</tr>
<tr>
<td>FBF, mL/min per 100 mL tissue</td>
<td>4.6±1.3</td>
<td>4.5±1.2</td>
</tr>
<tr>
<td>FVR, mm Hg · mL⁻¹ · min⁻¹ per 100 mL tissue</td>
<td>18.2±3.8</td>
<td>25.8±4.5*</td>
</tr>
</tbody>
</table>

All results are presented as mean±SD. *P<0.05 vs normotensive.

Blood pressures as well as FVR were significantly higher in the HPW group than in the NPW group. Other parameters were similar in the two groups. The FBF in HPW during reactive hyperemia was significantly lower than in NPW (Figure 1). In contrast, the increase in FBF after receiving sublingual NTG was similar in the two groups (Figure 2).

Study Protocol 2: Effects of ERT on Baseline Clinical Characteristics

The clinical characteristics both before and after the 12-week period for the NPW and HPW groups receiving ERT (ERT groups) and of the NPW and HPW groups not receiving ERT (control groups) are summarized in Table 2. The systolic and diastolic blood pressures and FVR were significantly higher in the HPW group than in the NPW group. These parameters were similar in the ERT and control HPW groups. The values for the other parameters were similar in the 4 groups. A 12-week period of ERT significantly decreased the concentrations of total cholesterol, LDL cholesterol and ACE activity and significantly increased PRA and the concentrations of estradiol and HDL cholesterol in the ERT groups. In contrast, there were no changes in the values of these parameters in the control groups. Changes in these parameters were similar in the two ERT groups. Other parameters, such as blood pressure, heart rate, basal FBF and FVR, and blood glucose remained unchanged after 12 weeks in the 4 groups.

Study Protocol 2: Effects of ERT on Forearm Resistance Artery Endothelial Function in NPW and HPW

After 12 weeks of ERT, the maximal FBF response to reactive hyperemia increased from 23.6±4.5 to 35.3±5.7 mL/min per 100 mL tissue (P<0.01) in the HPW group and from 30.8±3.6 to 36.2±5.9 mL/min per 100 mL tissue (P<0.01) in the NPW group (Figure 3), whereas no changes occurred in the control groups. The augmentation of the FBF response to reactive hyperemia evoked by ERT was significantly greater in the HPW group than in the NPW group (maximal FBF, 49±8 versus 17±5%, P<0.05). Changes in FBF after sublingual NTG administration were similar before and after the 12-week interval in the 4 groups (Figure 4).

Discussion

The FBF response to reactive hyperemia was significantly attenuated in the HPW group compared with the NPW, whereas the FBF response to NTG was similar in the two groups. Although long-term ERT augmented the FBF response to reactive hyperemia in NPW as well as HPW, the degree of augmentation of FBF in response to reactive hyperemia was significantly greater in the HPW group than in the NPW group. However, ERT did not alter the FBF response to NTG in the two groups.

It is well known that hypertension is associated with endothelial dysfunction. We and several other investigators...
have reported that endothelium-dependent vasorelaxation but not endothelium-independent vasodilation is impaired through blunted release of NO in hypertensive patients.\textsuperscript{10–12} We limited the present study to postmenopausal women. We found that endothelium-mediated vasorelaxation is attenuated in the forearm microvascular circulation of hypertensive postmenopausal women. Endothelial dysfunction is involved in the development of atherosclerosis. Therefore, the combination of menopause and hypertension may predispose to the development of CHD because of their effects on endothelial function.

There are several possible mechanisms by which long-term ERT enhances the FBF response to reactive hyperemia. Previous studies, including those from our laboratory, have shown that vascular response to reactive hyperemia in the forearm microvascular circulation are largely mediated by the release of NO from the vascular endothelium.\textsuperscript{16–18} In the present study, ERT decreased circulating ACE activity and increased PRA in postmenopausal women. These results are consistent with previous reports.\textsuperscript{19,20} It is hypothesized that the long-term ERT-induced increase in PRA is due to the inhibition of ACE activity, suggesting that the production of angiotensin II is prevented, whereas PRA is increased.\textsuperscript{21} A balance between the effects of angiotensin II and NO plays an important role in the regulation of vascular tone.\textsuperscript{22} Angiotensin II increases vascular superoxide production through activation of membrane-associated NADH/NADPH oxidase, resulting in the inactivation of NO and the production of toxic peroxynitrite.\textsuperscript{22} Therefore, the inhibition of ACE activity by ERT may increase the effects of NO by the inhibition of angiotensin II production. Endogenous bradykinin is regulated by ACE under physiological conditions. Bradykinin binds to B\textsubscript{2}-receptors on endothelial cells, causing the release of NO.\textsuperscript{23} The inhibition of ACE inhibits the degradation of bradykinin, resulting in increased NO release. In addition, the inhibited degradation of bradykinin induced by ACE inhibition has been shown to increase the production of prostacyclin and endothelium-derived hyperpolarizing factor.\textsuperscript{24} These vasodilating factors also augment reactive hyperemia in postmenopausal women.

It is well known that ERT has a beneficial effect on the lipid profile. Specifically, ERT increases the HDL cholesterol concentration, decreases the total and LDL cholesterol and lipoprotein concentrations, and protects LDL from oxidation.\textsuperscript{4,5} Oxidized LDL interferes with the formation of NO\textsuperscript{25} and directly inactivates NO.\textsuperscript{26} Several lines of evidence suggest that cholesterol-lowering and antioxidant therapies can restore forearm arterial endothelial function.\textsuperscript{27} Arnal et al\textsuperscript{28} confirmed that estrogen increases the release of bioactive NO by inhibiting the production of superoxide species in bovine endothelial cells. Although we did not directly measure oxidized LDL concentrations in the present study, the reduction in the LDL concentration may result in less suppression of NO formation by oxidized LDL.

A number of investigators have shown that estrogen directly upregulates the expression of endothelial NO synthase mRNA and protein, resulting in increased endothelial NO synthase activity and increased expression of NO synthase.\textsuperscript{29,30} The increase in endogenous NO production might contribute to enhanced vascular reactivity after ERT in

### Table 2. Clinical Characteristics of Postmenopausal Normotensive and Hypertensive Women Before and After ERT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive ERT Group (n = 10)</th>
<th>Normotensive Control Group (n = 10)</th>
<th>Hypertensive ERT Group (n = 8)</th>
<th>Hypertensive Control Group (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Body mass index, kg/m\textsuperscript{2}</td>
<td>22.7±2.7</td>
<td>22.8±2.9</td>
<td>23.1±2.5</td>
<td>23.0±2.6</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114.4±8.7</td>
<td>115.1±8.8</td>
<td>117.2±10.7</td>
<td>118.1±9.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67.8±6.9</td>
<td>66.7±6.7</td>
<td>69.8±8.9</td>
<td>71.2±8.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70.2±6.3</td>
<td>69.6±7.1</td>
<td>72.2±7.2</td>
<td>72.3±7.6</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.12±1.2</td>
<td>5.77±0.98*</td>
<td>6.09±1.31</td>
<td>6.03±1.28</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.54±0.74</td>
<td>1.49±0.67</td>
<td>1.58±0.79</td>
<td>1.53±0.86</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.72±0.38</td>
<td>2.05±0.28*</td>
<td>1.80±0.42</td>
<td>1.82±0.44</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.95±1.12</td>
<td>3.42±0.97*</td>
<td>3.98±1.23</td>
<td>3.90±1.19</td>
</tr>
<tr>
<td>Serum glucose, mmol/dL</td>
<td>4.8±0.4</td>
<td>4.9±0.6</td>
<td>4.8±0.6</td>
<td>4.7±0.6</td>
</tr>
<tr>
<td>Serum insulin, pmol/L</td>
<td>54.6±9.8</td>
<td>55.7±9.4</td>
<td>56.8±10.2</td>
<td>54.9±9.7</td>
</tr>
<tr>
<td>Plasma norepinephrine, pmol/L</td>
<td>1.35±0.87</td>
<td>1.29±0.93</td>
<td>1.41±1.17</td>
<td>1.38±0.97</td>
</tr>
<tr>
<td>PRA, ng/mL per hour</td>
<td>1.23±0.49</td>
<td>1.64±0.56*</td>
<td>1.35±0.59</td>
<td>1.22±0.53</td>
</tr>
<tr>
<td>Serum ACE activity, IU/L</td>
<td>12.8±3.4</td>
<td>10.7±2.9*</td>
<td>13.1±3.5</td>
<td>13.0±3.6</td>
</tr>
<tr>
<td>Estradiol, pmol/L</td>
<td>60.0±17</td>
<td>187±73</td>
<td>58.19</td>
<td>61.20</td>
</tr>
<tr>
<td>FBF, mL/min per 100 mL tissue</td>
<td>4.6±1.3</td>
<td>4.5±1.2</td>
<td>4.5±1.4</td>
<td>4.5±1.3</td>
</tr>
<tr>
<td>FVR, mm Hg · mL\textsuperscript{-1} · min\textsuperscript{-1} per 100 mL tissue</td>
<td>18.1±3.7</td>
<td>18.4±4.1</td>
<td>19.2±3.9</td>
<td>19.3±3.8</td>
</tr>
</tbody>
</table>

All results are presented as mean±SD.

\*P<0.05 vs before.

\†P<0.05 vs normotensive.
postmenopausal women, which may be mediated in part by an estrogen-dependent mechanism.

Norepinephrine, which acts as a potent vasoconstrictor, attenuates endothelium-dependent vasodilation. Du et al\textsuperscript{31} reported that ERT modulates autonomic nervous function. However, the plasma concentrations of norepinephrine were similar before and after ERT in the NPW and HPW groups in the present study. Therefore, the differences in the FBF response to reactive hyperemia after ERT in the two groups cannot be explained by differences in sympathetic nervous activity.

When we placed HPW on ERT, we selected patients with mild hypertension (stage I, based on the guidelines of JNC-VI\textsuperscript{14}). It is important that ERT improved endothelial dysfunction in the early stages of hypertension. In addition, we showed that the degree of restoration of forearm resistance artery endothelial function evoked by long-term ERT was greater in HPW than in NPW. The American Heart Association guidelines for primary prevention of CHD recommend that all postmenopausal women, especially individuals with additional cardiovascular risk factors, should receive ERT.\textsuperscript{32} Our data support their recommendations.

The precise mechanism responsible for the greater FBF response to reactive hyperemia after long-term ERT in HPW than in NPW remains unclear. In the present study, the degree of ERT-induced ACE inhibition was similar in NPW and HPW. Interestingly, Sumino et al\textsuperscript{20} have recently reported that ERT increases the plasma concentration of bradykinin to a greater extent in HPW than in NPW, whereas the ERT-induced reduction in serum ACE activity was similar in NPW and HPW. We hypothesize that HPW might have higher bradykinin concentrations after ERT, resulting in greater FBF responses to reactive hyperemia.

Because the reductions in total and LDL cholesterol concentrations by ERT were similar in NPW and HPW, the greater improvement in the FBF response to reactive hyperemia in HPW cannot be explained by differences in the effect of ERT on lipid profile. It has been reported that oxidative stress, an important cause of vascular injury, is increased in patients with essential hypertension.\textsuperscript{33} The greater effect of ERT on vascular reactivity in HPW may be due to differences in the degree of oxidative stress.

In the present study, ERT did not affect the blood pressure in either NPW or HPW. Our results are consistent with most studies showing no change in blood pressure with ERT in postmenopausal women.\textsuperscript{34,35} However, a small number of studies have reported conflicting results concerning the effects of ERT on blood pressure.\textsuperscript{36,37} The discrepancies in these studies may be explained by differences in the type of ERT and in the dose of estrogen. Although ERT enhanced endothelial function of the forearm resistance arteries in postmenopausal women in the present study, ERT had no effect on blood pressure, even in HPW.

This was not designed as a double-blind randomized placebo study. In addition, the number of subjects included, especially in the ERT study, is relatively small. Therefore, we cannot exclude the possibility that there is selection bias in the results.

The use of agonists to stimulate NO release, such as acetylcholine or bradykinin, as well as NO antagonists would allow us to draw more specific conclusions concerning the role of basal and stimulated NO production mediated by ERT in the forearm circulation. Recently, we have demonstrated that noninvasive methods, such as the measurement of FBF response to reactive hyperemia, can be used for assessing...
resistance vessel endothelial function instead of the intra-arterial vasoactive agent infusion method. 38 Indeed, this technique is simple and reproducible and does not cause adverse effects. Although it is thought that NO contributes to the FBF response to reactive hyperemia, we cannot deny the possibility that other factors including adiponectin, prostacyclin, and endothelium-derived hyperpolarizing factor are involved in estrogen-enhanced reactive hyperemia.

Conclusions
We showed that the degree of restoration of forearm resistance artery endothelial function induced by long-term ERT is greater in HPW than in NPW. These findings suggest that ERT has a beneficial effect on endothelial function not only in NPW but also in HPW, probably through enhanced NO bioactivity, resulting in a reduction in the risk of CHD. ERT may contribute to the reduction in the risk of CHD through mechanisms, including increased NO production, rather than through direct hypotensive effects in HPW. Our results also suggest that ERT may represent a new therapeutic intervention for endothelial dysfunction in patients with essential hypertension. Further investigation should be performed to determine the most suitable duration and dose of estrogen for restoring endothelial function in postmenopausal women.

Acknowledgments
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References


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