Estrogens, Progestins, and Heart Disease
Can Endothelial Function Divine the Benefit?
Robert A. Vogel, MD; Mary C. Corretti, MD

Coronary atherosclerosis is a prevalent, preventable, but slow disease. Demonstrating the clinical effect of an intervention requires at least 3 to 5 years, even in high-risk populations. Despite considerable supportive observational data, the value of hormone replacement therapy in the treatment of coronary heart disease in postmenopausal women remains uncertain.1-4 It is therefore very attractive to look for intermediate biological outcomes that may more quickly predict the results of event trials. One intermediate biological outcome, the anatomic progression of coronary atherosclerosis, has been shown to correlate with the incidence of cardiovascular events.5 Changes in angiographic disease progression, however, even with clinically successful interventions such as cholesterol lowering, do not occur in less than 1 to 2 years.6 The endothelium is thought to play an important role in the genesis of atherosclerosis, and changes in endothelial function have been reported within an hour of either estrogen administration or cholesterol lowering.7-9 If changes in endothelial function were found to predict the clinical benefit of interventions, then drug and lifestyle changes could be evaluated more rapidly. In this issue, Sorensen and coworkers10 report that cyclic estradiol and norethisterone hormone replacement therapy administered for 2.9±0.5 years did not improve endothelial function, measured as brachial artery flow-mediated vasodilation. The authors conclude that the addition of a progestin in a hormone replacement regimen may counteract the beneficial effects of estrogen alone on cardiovascular disease. If confirmed by other investigations, this study suggests that clinical trials of combined hormone replacement therapy will not find a beneficial effect on events and/or that endothelial function is not an appropriate intermediate biological outcome for assessing coronary heart disease therapy. Either finding would be an important observation.

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Although unproven, several lines of evidence suggest that the effect of an intervention on endothelial function might predict its impact on coronary disease progression and cardiovascular event rates. In 1980, Furchgott and Zawadzki11 demonstrated that the endothelium releases one or more local dilating factors. Subsequently, the endothelium has been found to be a complex endocrine and paracrine organ affecting vasoregulation, smooth muscle cell proliferation, platelet aggregation, monocyte adhesion, and thrombosis.6,12-17 Vaso-regulation occurs as a balance between the release of relaxing and constricting factors. The predominant relaxing factor is nitric oxide (or a nitric oxide adduct), which is synthesized from the amino acid l-arginine. Nitric oxide release activates smooth muscle cell guanylate cyclase, leading to increased cGMP production. Other relaxing factors include prostacyclin and hyperpolarizing factor, which operate through cAMP and potassium channels, respectively. The major constricting factors are endothelin-1, thromboxane, and prostaglandin H2. Under the burden of coronary risk factors, the endothelium increases production of oxygen free radicals, which combine with and deactivate nitric oxide.15

In addition to promoting vasodilation, normal endothelium has antiatherosclerotic and antithrombotic functions. It inhibits platelet aggregation, monocyte adhesion, vascular smooth muscle cell proliferation, and thrombosis, all of which are important factors in the development of atherosclerosis and plaque disruption.6,12,14-16 In contrast, dysfunctional endothelium upregulates chemotactic and adhesion molecules for monocytes and T lymphocytes and secretes colony-stimulating factors that induce differentiation of monocytes into macrophages. As part of the atherosclerotic process, the latter take up modified cholesterol in an unregulated fashion via scavenger receptors, creating the metabolically active foam cells. Dysfunctional endothelium promotes platelet aggregation through decreased nitric oxide availability and promotes thrombosis through a decreased ratio of tissue plasminogen activator to plasminogen activator inhibitor-1.4 In vitro, dysfunctional human endothelial cells exhibit a prothrombotic state, characterized by increased tissue factor activity and reduced activation of protein C. Experimental models of atherosclerosis demonstrate an inverse correlation of nitric oxide availability and disease development. Reducing nitric oxide availability through a synthase inhibitor (Nω-nitro-l-arginine methyl ester) increases the development of atherosclerosis, whereas increasing its availability through the administration of l-arginine decreases its development, at least transiently.17,18 These data suggest an important role for the endothelium in the prevention and promotion of atherosclerosis.

Endothelial function can be clinically assessed through measurements of endothelium-dependent vasodilation and plasma markers such as endothelin-1, von Willebrand factor, thrombomodulin, and monocytes adhesion molecules. Endothelial function is most commonly assessed as a vasodilatory
response to pharmacological or mechanical stimuli. Numerous endothelium-dependent agonists have been identified, including acetylcholine, serotonin, bradykinin, thrombin, and substance P. Each acts through a membrane receptor with signal transduction operating through G proteins. Alternatively, increased blood flow shear (flow-mediated) is a mechanical means to stimulate vasodilation through nitric oxide release. Endothelium-dependent vasodilation has been studied in both the coronary and peripheral circulations. Change in vessel diameter is used as an index of conductance vessel function, and change in blood flow is used as an index of resistance vessel function. The three most commonly used clinical measures are quantitative coronary arteriographic diameter changes in response to varying concentrations of acetylcholine, high-frequency ultrasound assessed brachial artery diameter changes after blood pressure cuff–induced hyperemia, and venous plethysmographic changes in forearm blood flow after infusions of various concentrations of acetylcholine. An assessment of non–endothelium-dependent vasodilation by use of nitroglycerin or nitroprusside is usually performed concomitantly to measure nonspecific smooth muscle effects. Acetylcholine-induced coronary vasodilation has been shown to correlate significantly with brachial artery flow–mediated vasodilation.

Measurements of endothelium-dependent vasodilation vary depending on vessel location and assessment technique. Especially in the setting of atherosclerosis, responses vary regionally, even in the same vessel. In conductance vessels, distal sites and smaller vessels tend to be more vasoactive than proximal sites and larger vessels. Nitric oxide availability appears to play a more important role in basal and stimulated vasoregulation in conductance vessels than in resistance vessels. Coronary risk factors such as hypercholesterolemia may affect the vasodilatory responses to only certain endothelium-dependent agonists. These confounding technical factors must be considered before endothelial function is used as an intermediate biological outcome for coronary heart disease.

The initial clinical studies found impaired endothelial function in angiographically diseased arteries and in normal vessels in patients with atherosclerosis elsewhere, leading to the concept that endothelial dysfunction occurs very early in the disease process. More recently, endothelial dysfunction in both the coronary and brachial arteries has been found to be associated with the presence of the traditional coronary risk factors, independent of even intravascular ultrasound evidence of atherosclerosis. An attractive current hypothesis is that endothelial function serves as an integrating index of overall coronary risk factor stress. This may explain some of the failure of the current study to demonstrate a beneficial effect on endothelial function, as the incidences of smoking and hypercholesterolemia were high in the women studied. Several risk factor and drug interventions that have been shown to reduce cardiovascular event risk have also been demonstrated to improve endothelial function. For example, 10 of 11 reported cholesterol-lowering trials have shown improvements in brachial or coronary endothelial function. The close associations between the presence of well-established risk factors and endothelial function support but do not establish the predictiveness of endothelial function as an intermediate biological outcome.

Premenopausal women have increased endothelium-dependent vasodilation compared with men, although their smaller arteries may contribute to this finding. Endothelial function, measured as brachial artery flow–mediated vasodilation, begins to decline after 50 to 55 years of age compared with 40 years of age in men, again suggesting a beneficial effect of naturally occurring estrogens and progestins. Improvements in endothelium-dependent vasodilation have been demonstrated with estrogen administered orally, intravenously, and intra-arterially to postmenopausal women. Changes have been observed within 15 minutes of intravenous administration and last at least 9 weeks. The predominant mechanism appears to be an upregulation of the transcription of nitric oxide synthase. In nonhuman primates, estrogen has been shown to improve endothelium-mediated vasodilation in ovariectomized normocholesterolemic and hypercholesterolemic animals. Unlike other interventions, estrogen has been found to increase basal arterial diameter and decrease basal vascular resistance. In women with risk factors, it has also been shown to increase vasodilation to the non–endothelium-dependent mediator nitroprusside. Although some studies have not shown an effect in men, two recent trials of long-term estrogen administration in high doses to transsexual men demonstrated increases in brachial artery flow–mediated vasodilation. Importantly, increases in endothelium-dependent vasodilation in men correlated with decreases in testosterone levels. In experimental models, progestins tend to oppose the effects of estrogen on endothelial function. Observational data suggest that postmenopausal women on a variety of hormone replacement regimens have slightly improved endothelial function, but prospective trials of specific regimens have not been reported other than the current study. The effect of progestins on endothelial function is important in predicting the clinical effects of hormone replacement therapy because only 25% to 50% of the

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**Factors Associated With Endothelial Dysfunction and Interventions Demonstrated to Improve Endothelial Function**

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<thead>
<tr>
<th>Factors Associated With Endothelial Dysfunction</th>
<th>Interventions Improving Endothelial Function</th>
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<tbody>
<tr>
<td>Increased age</td>
<td>l-Arginine</td>
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<tr>
<td>Male sex</td>
<td>Estrogen</td>
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<tr>
<td>Family history of CHD</td>
<td>Antioxidants</td>
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<tr>
<td>Smoking</td>
<td>Smoking cessation</td>
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<tr>
<td>Increased cholesterol</td>
<td>Cholesterol lowering</td>
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<td>Low HDL cholesterol</td>
<td>ACE inhibitors</td>
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<td>Hypertension</td>
<td>Exercise</td>
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<td>Diabetes mellitus</td>
<td>Homocysteine lowering</td>
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<td>Obesity</td>
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<td>High-fat meal</td>
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<td>Increased homocysteine</td>
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CHD indicates coronary heart disease.
reduction in cardiovascular events achieved with estrogen therapy can be attributed to lipid changes.32,33 It has been assumed that the predominant effect is a direct arterial one, possibly through improvements in endothelial function.

Estrogen and progestin administration have numerous effects on other markers of endothelial function, coagulation parameters, and lipoproteins that may affect the atherosclerotic process. Estrogen administration lowers LDL cholesterol and raises HDL cholesterol, both of which are associated with improved endothelial function.32–34 Estrogen also lowers lipoprotein(a) and increases VLDL and triglycerides, but these are thought to have lesser effects on endothelial function. In the Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial, all hormone regimens lowered LDL cholesterol, but medroxyprogesterone acetate attenuated the estrogen-induced increase in HDL cholesterol.34 Similar effects were observed in the current study. Estrogen replacement therapy also increases the production of prostacyclin, decreases thromboxane and endothelin-1 levels, and blocks endothelin receptors. Other favorable effects of estrogen include decreases in fibrinogen and plasminogen activator inhibitor-1 and increases in plasminogen and insulin sensitivity. It is also an antioxidant and decreases oxygen free radicals in the arterial wall. Unfavorable coagulation effects of estrogen include decreases in antithrombin III and increases in factors VII and X.

Although epidemiological and observational data suggest that hormone replacement therapy is associated with a reduction in cardiovascular disease risk, most data are with estrogen administration alone, and no large randomized trials have been reported yet. In the Framingham Heart Study, early menopause was associated with a fourfold increase in cardiovascular disease. Thirteen case-controlled and 17 prospective cohort observational studies have generally found a protective effect of estrogen.1–4 In the 59,337-woman Nurses’ Health Study, hormone replacement therapy was associated with a relative risk for major coronary heart disease events of 0.39 (0.19 to 0.78) compared with nonusers, which was statistically similar to the benefit from estrogen use alone.35,36 In this study, the benefit on survival of hormone replacement therapy decreased with duration of therapy because of an increase in breast cancer and appeared lower in those women with lower cardiovascular risk. For a definite understanding of the clinical benefit of hormone replacement therapy, we await the results of several large randomized ongoing trials, including the Heart and Estrogen/Progestin Replacement Study (HERS) to be reported about the year 2000 and the Women’s Health Initiative to be reported about the year 2005. In addition to providing objective data on this important clinical decision, the results of these trials will help us understand the value of endothelial function as a divining intermediate biological outcome.

References


**KEY WORDS:** Editorials ■ endothelium ■ heart diseases ■ hormones
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