Hormone Replacement Therapy and Endothelial Function
The Exception That Proves the Rule?

Joseph A. Vita, John F. Keaney, Jr

The endothelium plays a central role in the regulation of vascular homeostasis by releasing paracrine factors that influence vascular tone, thrombosis, and inflammation in the arterial wall. A principal endothelial product responsible for homeostasis is nitric oxide (NO), which is synthesized by the endothelial isoform of NO synthase in response to a number of stimuli, including increased shear stress that accompanies increased arterial flow. Atherosclerosis and its risk factors are characterized by an impairment of endothelial NO-dependent vasodilation, and the magnitude of this defect in the coronary circulation predicts cardiovascular disease events, raising the possibility of a pathogenic relationship.

This notion of a causal relation between endothelial dysfunction and cardiovascular events is also supported by intervention data. For example, lipid-lowering therapy, angiotensin-converting enzyme inhibition, smoking cessation, and exercise all reverse endothelial dysfunction and have proven beneficial against cardiovascular disease events. This concordance between improved endothelial function and reduced cardiovascular events has prompted speculation that changes in endothelial function are partially responsible for the benefits. Thus, endothelial dysfunction could potentially be used as a surrogate marker for cardiovascular disease risk in study of risk reduction therapies.

Hormone replacement therapy has received considerable attention as a means for primary and secondary prevention of cardiovascular disease. This interest was initially based on population-based studies linking a reduced incidence of cardiovascular disease to hormone replacement therapy. Estrogen has many potential benefits, including favorable influence on serum lipids and thrombotic factors, and there is substantial evidence that chronic estrogen treatment also improves endothelial function in postmenopausal women (Table). Despite these apparent benefits, a relatively large-scale randomized clinical trial of hormone replacement therapy (conjugated equine estrogen plus medroxyprogesterone acetate) for secondary prevention of cardiovascular disease (HERS) failed to demonstrate a benefit from estrogen. Furthermore, in a separate study, neither the combination of estrogen and progesterone nor estrogen alone had any effect on angiographic extent of coronary artery disease. As a consequence of these findings, a consensus panel concluded that hormone replacement therapy has no role in either the primary or secondary prevention of cardiovascular disease, pending the results of ongoing clinical trials. These data highlight an apparent lack of concordance between the effects of estrogen treatment on endothelial function and clinical outcome, fueling speculation against the clinical relevance of endothelial function.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Herrington and colleagues report the effect of hormone replacement therapy on endothelium-dependent vasodilation in 1662 women participating in the Cardiovascular Health Study, a longitudinal study of cardiovascular risk factors in the elderly. The authors used vascular ultrasound to measure flow-mediated dilation of the brachial artery, a response that has been shown to be NO-dependent and to correlate with responses in the coronary circulation. As with the coronary circulation, endothelial dysfunction in the brachial artery improves with many risk reduction therapies, and a preliminary study suggests that brachial artery endothelial dysfunction is an independent predictor of short-term cardiovascular disease events in high risk patients.

Overall, Herrington and colleagues found no significant difference in endothelium-dependent vasodilation in the 291 women with current or previous hormone replacement therapy (largely unopposed estrogen) compared with the women who had never received replacement therapy. When the subjects’ data were stratified according to current versus previous therapy, or to unopposed estrogen versus estrogen-progesterone combination therapy, the results were unchanged. Interestingly, when the patients were stratified according to age, the presence of cardiovascular disease, cardiovascular medication use, and risk factors, there was a benefit of hormone replacement therapy that was restricted to younger, lower-risk women. The authors concluded that the beneficial effects of estrogen might be limited to women without established cardiovascular disease. The strengths of the study include the large, well-characterized patient cohort, the careful and well-validated methodology for assessment of brachial vasodilation, and the rigorous statistical approach.

How do these findings relate to the HERS results? The women in the study by Herrington et al were substantially older than women in other studies of hormone replacement therapy and endothelial function. In contrast to all previous studies except one that involved only 4 subjects, this study is the only one that included patients with known cardiovascular...
Studies of Chronic Hormone Replacement Therapy and Endothelial Function in Postmenopausal Women

<table>
<thead>
<tr>
<th>First Author</th>
<th>N</th>
<th>Age (years)</th>
<th>Medical Conditions</th>
<th>Rx</th>
<th>Endpoint</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Lieberman</td>
<td>13</td>
<td>55±7</td>
<td>Healthy women with no CVD or risk factors</td>
<td>Oral estrogen</td>
<td>FMD</td>
<td>+</td>
</tr>
<tr>
<td>Herrington</td>
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<td>Postmenopausal</td>
<td>Coronary artery disease and angina</td>
<td>Oral or topical estrogen</td>
<td>Intracoronary acetylcholine</td>
<td>+</td>
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<tr>
<td>Rosselli</td>
<td>13</td>
<td>&gt;45</td>
<td>Healthy women</td>
<td>Topical estrogen</td>
<td>Plasma NO₂/NO₃</td>
<td>+</td>
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<tr>
<td>McCrohon</td>
<td>55</td>
<td>58±3</td>
<td>Healthy women</td>
<td>Estrogen alone</td>
<td>Plasma NO₂/NO₃</td>
<td>−</td>
</tr>
<tr>
<td>Gerhard</td>
<td>17</td>
<td>60 (48–70)</td>
<td>Healthy women with no CVD or risk factors</td>
<td>Topical estrogen</td>
<td>FMD</td>
<td>+</td>
</tr>
<tr>
<td>Sorensen</td>
<td>46</td>
<td>53±3</td>
<td>Healthy women with no CVD or risk factors</td>
<td>Oral estrogen + oral norethisterone</td>
<td>FMD</td>
<td>−</td>
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<tr>
<td>Bush</td>
<td>17</td>
<td>56±9</td>
<td>No CVD</td>
<td>Estrogen and estrogen/progesterone</td>
<td>FMD</td>
<td>+</td>
</tr>
<tr>
<td>Arora</td>
<td>11</td>
<td>53 (43–58)</td>
<td>Healthy women</td>
<td>Estrogen</td>
<td>Skin microvessel acetylcholine</td>
<td>+</td>
</tr>
<tr>
<td>Koh</td>
<td>28</td>
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<td>Estrogen</td>
<td>FMD</td>
<td>+</td>
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<tr>
<td>Koh</td>
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<td>55±8</td>
<td>Healthy women</td>
<td>Estrogen + progesterone</td>
<td>FMD</td>
<td>+</td>
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<tr>
<td>Wakatsuki</td>
<td>14</td>
<td>53 (45–65)</td>
<td>Healthy women</td>
<td>Oral estrogen</td>
<td>FMD</td>
<td>+</td>
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<tr>
<td></td>
<td>31</td>
<td></td>
<td></td>
<td>Oral estrogen + oral medroxyprogesterone</td>
<td>FMD</td>
<td>−</td>
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<tr>
<td>Herrington</td>
<td>291</td>
<td>70–80+</td>
<td>Elderly women</td>
<td>HRT (76% unopposed oral estrogen)</td>
<td>FMD</td>
<td>−</td>
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<tr>
<td></td>
<td>32</td>
<td></td>
<td></td>
<td>Women with no risk factors, CVD, or meds</td>
<td>FMD</td>
<td>+</td>
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<tr>
<td>Hulley</td>
<td>2763</td>
<td>67±7</td>
<td>Coronary artery disease</td>
<td>Oral estrogen + medroxyprogesterone</td>
<td>Cardiovascular events</td>
<td>−</td>
</tr>
</tbody>
</table>

N indicates number of women receiving treatment; CVD, cardiovascular disease; FMD, brachial artery flow-mediated dilation; NO₂/NO₃, total nitrite and nitrate; meds, cardiac medications; HRT, hormone replacement therapy.

disease (Table). Thus, the subjects were much more comparable to the HERS patient population, and the results are parallel. When women without cardiovascular disease or cardiovascular disease risks were considered, the results from Herrington and colleagues³ are similar to previous studies of chronic unopposed estrogen and endothelial function. It remains unclear why older women with established cardiovascular disease would have a reduced response to estrogen treatment, but as pointed out by the authors, there currently is evidence for reduced expression of the estrogen receptor in women with advancing age and with cardiovascular disease.³¹ Although the current study showed no effect of progesterone therapy on endothelial function, many of the previous studies suggest that inclusion of medroxyprogesterone reduces or eliminates the benefits of estrogen, and these findings also are concordant with HERS.

The study by Herrington and colleagues³ has several limitations. First, it was observational in nature and not a randomized trial. Thus, the hormone combination and duration of treatment varied, and many women were no longer receiving therapy at the time of the ultrasound study. Second, given the overall negative result, the subgroup analysis showing a benefit in younger, healthier subjects must be considered exploratory in nature. Third, the small number of subjects in certain subgroups limits the findings. For example, only 32 women had no cardiovascular disease, risk factors, or cardiovascular medication use, and a relatively small number of patients were receiving estrogen and progesterone in combination. Finally, the degree of brachial artery dilation was rather low compared with previous studies. As the authors acknowledge, this discrepancy is likely related to the older subject age, the lower arm cuff position, and the use of a 4-minute, rather than 5-minute period of cuff occlusion to induce hyperemia. Despite these limitations, this study represents a relatively large-scale and careful study of the effects of hormone replacement therapy on endothelial function in older, higher risk women.

Thus, when a more comparable population is studied, the effects of hormone replacement therapy on endothelial function do seem to parallel the HERS results, supporting the utility of endothelial function as a surrogate endpoint. The available endothelial function studies would predict a bene-
ficial effect of unopposed estrogen for the primary prevention of cardiovascular disease in healthy women that are closer to menopause. This question will be addressed in ongoing clinical trials, including the Women’s Health Initiative. If it turns out that unopposed estrogen has benefit, any clinical recommendations will have to be considered carefully, because of the potential for pro-carcinogenic effects of unopposed estrogen. It remains quite conceivable that these and other adverse effects will outweigh any beneficial effects on the vasculature. Use of newer selective estrogen receptor modulations (SERMs) may be another way to take advantage of the benefits of estrogen without inducing its adverse effects. These agents have already been shown to have beneficial effects on endothelial function, and thus would be predicted to have benefit against cardiovascular disease.

References


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