Arterial intima-media thickness: site-specific associations with HRT and habitual exercise

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CARDIOVASCULAR DISEASE (CVD) is the leading cause of death in women in Westernized societies (3). Postmenopausal women have a higher incidence of CVD than premenopausal women, presumably due in part to the loss of endogenous estrogen production. Observational studies have demonstrated that the risk for CVD is lower in postmenopausal women who take hormone replacement therapy (HRT) (24, 25, 54) and who perform regular physical activity (36, 40). The cardioprotective effects of HRT and regular exercise are thought to be due in part to improvements in traditional atherosclerotic risk factors (e.g., blood lipids) (26). However, emerging evidence points toward other mechanisms of action, including direct effects on the arterial wall (30, 48). In this context, high-resolution ultrasonography, a valid and reliable measure, allows for noninvasive in vivo determination of the structure and function of large arteries (50). Increased arterial wall intima-media thickness (IMT), measured by B-mode ultrasonography, is associated with a higher prevalence of coronary and peripheral atherosclerosis (1, 7, 37) and with an increased risk for myocardial infarction and stroke (46). As such, in postmenopausal women, HRT use and/or habitual exercise could exert their protective influences on CVD in part via suppression of IMT. However, there is limited information regarding this possibility.

It is well known that there are major differences in the geometry and properties of various arterial segments (5, 53). The arterial tree includes both large elastic (e.g., carotid) and predominantly muscular (e.g., femoral) arteries. It is not known whether the influence of lifestyle interventions on arterial wall structure differs between elastic and muscular vessels. This is important considering recent observations that femoral IMT is a better predictor of coronary atherosclerosis than carotid IMT (37, 43).

Accordingly, in the present study we tested the following hypotheses. First, the use of HRT would have the smallest IMT in their large arteries. Second, large-artery IMT would be smaller in postmenopausal women who perform habitual aerobic exercise. Third, women who practice both regular exercise and use HRT would have the smallest IMT in their large arteries. In addition, to determine whether the influence of HRT and/or habitual exercise is site specific, we measured IMT in both the carotid and femoral arteries.
Methods

Subjects. Seventy-seven healthy postmenopausal (absence of menses ≥1 yr) women aged 48–80 yr participated in this study. Subjects were classified according to HRT use (HRT or no HRT) and habitual exercise (endurance trained or sedentary) status. Endurance-trained women had been performing regular aerobic exercise (primarily running) an average of 58 ± 4 min/day, 5.1 ± 0.3 days/wk for at least 5 yr (range 5–60 yr) and were active in local road-running races. Sedentary women did not perform any type of regular exercise >2 days/wk. HRT users (n = 43; 23 sedentary and 20 endurance trained) had been following their regimen for an average of 10 ± 1 yr and were taking either an oral preparation of conjugated estrogens (Premarin; 15 sedentary and 8 endurance trained), oral estradiol (6 sedentary and 7 endurance trained), or transdermal estradiol (2 sedentary and 5 endurance trained). Twenty-three of the HRT users (13 sedentary, and 10 endurance trained) were taking a combination of estrogen and progestins (e.g., medroxyprogesterone acetate). Nonusers of HRT had not taken any estrogen preparations for at least 2 years. All groups were matched for age, menopause duration, and years of education. Within each physical activity classification (endurance trained or sedentary) users and nonusers of HRT were matched for maximal aerobic capacity, CVD risk factors, and duration of HRT use.

To be consistent with our research focus on primary aging, we recruited healthy postmenopausal women. Subjects were included if they were normotensive (31), nonsmokers, and were free of overt chronic diseases as assessed by medical history, physical examination, standard blood chemistries, hematural evaluation (e.g., blood glucose <7 mmol/l) (2), and treadmill exercise stress test (21). Subjects who demonstrated significant IMT (>1.5 mm), plaque formation (28), ankle-brachial pressure index <0.90 (23), and/or characteristics of atherosclerosis were excluded. All subjects gave written informed consent to participate. All procedures were reviewed and approved by the Human Research Committee.

Measurements. All measurements were performed after a 4-h fast (12 h for determination of metabolic parameters) and abstinence from caffeine. Endurance-trained women were tested 20–24 h after their last training session to avoid any acute effects of exercise. During the experimental sessions, subjects were examined after 20 min of supine rest in a quiet, temperature-controlled room.

Carotid and femoral artery IMT. Common carotid and femoral artery IMT were measured from longitudinal two-dimensional B-mode images derived from an ultrasound machine (model SSH-140, Toshiba) equipped with a high-resolution linear-array transducer (7.5 MHz) as originally described by Pignoli et al. (50) and more recently by our laboratory (13, 14, 57). B-mode measurements of IMT obtained in vivo have been validated against both B-mode in vitro imaging and histological determinations, thus demonstrating that this technique is a useful and valid approach for the measurement of IMT of human arteries in vivo (50, 61). The images were recorded on a super-VHS recorder (model AG7350, Panasonic) for later off-line analysis and were digitized with a video frame grabber (model DT-3152, Data Translation) and stored in a personal computer. All scans were performed by the same ultrasonographer.

Carotid and femoral artery ultrasound images were analyzed for IMT and lumen diameters with the use of computerized image analysis software, as previously described (13, 14, 50, 57, 58). The spatial resolution using the 7.5-MHz transducer used in the present study was 0.3 mm. However, at distances >0.3 mm, the minimum difference detectable when our ultrasound images were interfaced with our image analysis software is 0.07 mm (14, 58). All images were analyzed by the same investigator, who was blinded to the group assignment of the subjects. IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-external elastic interface (50). Because the near-wall IMT cannot be precisely measured on a consistent basis (50), lumen diameter was measured as the distance between the vessel far-wall boundary corresponding to the interface between the lumen and intima and a near-wall boundary corresponding to the interface of the adventitia and media. All measurements were made at end diastole as previously described (50). At least 10 measurements of IMT and lumen diameter were taken at each segment, and the mean values of these 10 measurements were used for analysis. Wall thickness was normalized for lumen size and was expressed as IMT/lumen diameter ratio. In our laboratory, this technique has excellent day-to-day reproducibility for both carotid and femoral IMT and lumen diameter (3 ± 1% coefficient of variation) (13, 57).

Blood viscosity and arterial wall shear stress. Whole blood viscosities were measured at shear rates of 0.5–60 revolutions/min (rpm) at 37°C using a cone and plate viscometer (model DV-1+, Brookefield) in 15 sedentary no HRT, 19 sedentary HRT, 12 endurance-trained no HRT, and 18 endurance-trained HRT, as previously described (14, 55). Blood viscosity at shear rates of 60 rpm (i.e., the highest revolution) were used to calculate femoral and carotid artery wall shear stress based on the following formula as previously described (9, 15): \( \frac{4\eta V_m}{D} \), where \( \eta \) is blood viscosity (in mPa·s), \( V_m \) is mean blood velocity (in cm/s), and \( D \) is arterial diameter (in cm).

Brachial arterial blood pressure and tangential wall stress. Peripheral arterial blood pressure was measured with a semiautomated device (Dinamap, Johnson and Johnson) over the brachial artery, as previously described (13, 57, 58). Tangential wall stress (dyn/cm²) was calculated using \( \left( \frac{MBP \times D}{2\times IMT} \right) \), where MBP is mean blood pressure (dyn/cm²), \( D \) is diameter in centimeters, and IMT is expressed in centimeters (14, 35).

Metabolic risk factors and estradiol. Fasting plasma concentrations of cholesterol, glucose, insulin, and estradiol were measured in the clinical laboratory affiliated with the University of Colorado Adult General Clinical Research Center, as previously described (55).

Body composition and leg tissue mass. Total fat mass, fat-free mass, and bone density were determined with dual-energy X-ray absorptiometry (model DPX-IQ, Lunar). Total fat mass and fat-free mass of the right leg were determined from regional analysis from the whole body dual-energy X-ray absorptiometry scan using bony landmarks as previously described (12).

Maximal oxygen consumption. A modified Balke incremental treadmill exercise protocol was used to determine maximal oxygen consumption, a measure of maximal aerobic exercise capacity (56).

Statistical analysis. Two-way ANOVA was used to assess the effects of HRT and endurance-training status. In the case of a significant F value, a Newman-Keuls post hoc test identified differences among group means. Univariate correlation analyses were used to determine the relations between variables of interest. One-way analysis of covariance (ANCOVA) was used to examine the contribution of the correlated variables to differences in IMT. All data are reported as means ± SE. Statistical significance was set at \( P < 0.05 \).
RESULTS

There were no significant group differences in age, menopause duration, years of education, height, leg fat-free mass, brachial artery blood pressure, high-density lipoprotein (HDL) cholesterol, or fasting glucose concentrations (Table 1). Body mass, body mass index, percent body fat, total leg mass, resting heart rate, blood viscosity, total and low-density lipoprotein (LDL) cholesterol were lower, and maximal oxygen uptake was higher in endurance-trained compared with sedentary women \((P < 0.05)\). Estradiol levels were higher \((P < 0.05)\) and blood viscosity tended to be lower \((P = 0.06)\) in users compared with nonusers of HRT. Fasting plasma insulin concentration was higher in sedentary no-HRT women compared with the other three groups \((P < 0.01)\).

Table 2. Characteristics of femoral and carotid arteries in sedentary and endurance-trained postmenopausal women by HRT status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sedentary</th>
<th>Endurance Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Femoral artery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen diameter, mm</td>
<td>8.4 ± 0.3</td>
<td>8.3 ± 0.2</td>
</tr>
<tr>
<td>IMT/lumen diameter</td>
<td>0.069 ± 0.003</td>
<td>0.062 ± 0.002</td>
</tr>
<tr>
<td>Lumen diameter/total leg mass, mm/kg</td>
<td>0.74 ± 0.05</td>
<td>0.78 ± 0.06</td>
</tr>
<tr>
<td>Shear stress, dyn/cm²</td>
<td>1.5 ± 0.1</td>
<td>1.9 ± 0.2*</td>
</tr>
<tr>
<td>Tangential stress, 10⁶ dyn/cm²</td>
<td>8.6 ± 0.5</td>
<td>9.0 ± 0.7</td>
</tr>
<tr>
<td><strong>Carotid artery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen diameter, mm</td>
<td>6.5 ± 0.1</td>
<td>6.2 ± 0.1*</td>
</tr>
<tr>
<td>IMT/lumen diameter</td>
<td>0.096 ± 0.003</td>
<td>0.097 ± 0.002</td>
</tr>
<tr>
<td>Shear stress, dyn/cm²</td>
<td>4.9 ± 0.2</td>
<td>5.3 ± 0.3</td>
</tr>
<tr>
<td>Tangential stress, 10⁶ dyn/cm²</td>
<td>6.0 ± 0.2</td>
<td>5.9 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. IMT, intima-media thickness. *\(P < 0.05\) vs. sedentary; †\(P < 0.05\) vs. no HRT; ‡\(P < 0.05\) vs. sedentary no HRT.
not diminish the differences between endurance-trained and sedentary no HRT; however, the difference between sedentary HRT and sedentary no HRT was no longer significant (P = 0.10). Femoral shear stress was higher in HRT users compared with nonusers (P < 0.05; Table 2), but was lower in endurance-trained compared with sedentary women (P < 0.05). Tangential wall stress was higher in endurance-trained women, regardless of HRT status (P < 0.05; Table 2).

For the carotid artery, HRT use, but not endurance-training status, was associated with a smaller lumen diameter (P < 0.05; Table 2). In contrast to the femoral artery, carotid IMT or IMT/lumen ratio were not significantly associated with HRT or endurance-training status (Fig. 1B; P = 0.15 and 0.09, respectively; Table 2). Carotid artery shear stress tended to be higher in HRT users (P = 0.08; Table 2), but was not different by endurance-training status. Tangential wall stress was similar across the groups. The type of HRT used (unopposed estrogen or combined estrogen and progestin) was not associated with femoral or carotid artery structures.

Because the effects of HRT on carotid IMT may not manifest until later years (18, 42, 59), we sought to determine the effects of age and HRT on arterial IMT by dividing the study population into subgroups of younger (<65 yr) and older (≥65 yr) postmenopausal women by HRT status. Subject characteristics for these subgroup analyses are listed in Table 3. Total leg mass, fasting insulin concentration, blood viscosity, and carotid systolic blood pressure were lower (all P < 0.05), and plasma estradiol higher (P < 0.001) in users compared with nonusers of HRT, regardless of age group. In subgroups of women <65 and ≥65 yr, carotid IMT was smaller in the HRT users (P < 0.05 compared with no HRT) and was similar (P = 0.21) to values in the younger postmenopausal women (Fig. 2). Carotid diameter was smaller in HRT users compared with no HRT.

Fig. 1. Femoral (A) and carotid (B) intima-media thickness (IMT) in postmenopausal women according to hormone replacement therapy (HRT) use and endurance-trained status. *P < 0.005 vs. sedentary no HRT; †P < 0.001 vs. sedentary no HRT.

Table 3. Selected subject characteristics in subgroups of women <65 and ≥65 yr by HRT status

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;65 Yr</th>
<th>≥65 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>55 ± 1</td>
<td>71 ± 1*</td>
</tr>
<tr>
<td>Sed/ET, n</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Menopause duration, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>165 ± 1</td>
<td>164 ± 1</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>66.9 ± 3.8</td>
<td>65.7 ± 2.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.1 ± 0.8</td>
<td>25.0 ± 0.9</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>30 ± 2</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>Total leg mass, kg</td>
<td>11.0 ± 0.6</td>
<td>10.7 ± 0.4†</td>
</tr>
<tr>
<td>Leg fat-free mass, kg</td>
<td>6.9 ± 0.2</td>
<td>6.4 ± 0.1</td>
</tr>
<tr>
<td>Brachial systolic BP, mmHg</td>
<td>116 ± 3</td>
<td>114 ± 2</td>
</tr>
<tr>
<td>Brachial diastolic BP, mmHg</td>
<td>69 ± 2</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.2 ± 0.4</td>
<td>5.2 ± 0.2</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.6 ± 0.1</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>3.1 ± 0.3</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td>Fasting insulin, µU/ml</td>
<td>6.4 ± 1.5</td>
<td>5.0 ± 0.4†</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.0 ± 0.2</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>Plasma estradiol, pmol/l</td>
<td>52 ± 7</td>
<td>331 ± 72†</td>
</tr>
<tr>
<td>Blood viscosity, mPa·s</td>
<td>4.36 ± 0.11</td>
<td>4.15 ± 0.08‡</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. Sed, sedentary; ET, endurance trained. *P < 0.05 vs. <65 yr; †P < 0.05 vs. no HRT.
HRT, regardless of age group. Carotid IMT/lumen ratio was lower in women <65 yr compared with ≥65 yr no HRT (P < 0.05; Table 4). Carotid shear and tangential stress were not different among the subgroups. Endurance training status was not associated with carotid IMT in this subgroup of older women (P > 0.05; data not shown) but was associated with a lower femoral IMT (P < 0.005; data not shown).

Physiological correlates of femoral and carotid IMT. In the pooled population, femoral IMT was related to maximal oxygen consumption (r = −0.51), age (r = 0.45), menopause duration (r = 0.33), and fasting plasma insulin concentration (r = 0.28) (all P < 0.05). Carotid IMT was associated with age (r = 0.42), menopause duration (r = 0.46), and maximal oxygen consumption (r = −0.30) (all P < 0.05). No other variables were significantly related to femoral or carotid IMT.

When ANCOVA was performed with maximal oxygen consumption as the covariate, endurance training-related differences in femoral IMT and femoral diameter no longer were significant (P = 0.88 and P = 0.06). However, HRT-related differences remained highly significant (P < 0.001) after such adjustment. Covarying femoral IMT for the other significant correlates did not influence the main effects of endurance training or HRT.

DISCUSSION

The primary findings of the present study are as follows. First, healthy postmenopausal women who use HRT have a smaller femoral IMT compared with non-users of HRT. However, the relation between HRT and carotid IMT is only evident in women aged ≥65 yr. Second, postmenopausal women who perform regular endurance exercise have a smaller femoral but not carotid IMT compared with sedentary women. Third, the lowest mean IMT is observed in women who are both endurance trained and users of HRT. Finally, HRT and endurance-training associated group differences are not related to traditional atherosclerotic risk factors. These results suggest that among healthy postmenopausal women, HRT use and habitual exercise are similarly associated with a smaller arterial wall thickness, and that these effects are clearly evident only in predominantly muscular arteries. The site-specific relations may be due to differences between muscular and elastic arteries in smooth muscle cell content, plasticity, and/or heterogeneous influences on the arterial wall.

We found that postmenopausal women who perform regular vigorous endurance exercise have a smaller femoral but not carotid IMT. The 13% smaller femoral IMT in our endurance-trained women compared with their age-matched sedentary counterparts is equivalent to the mean differences that we reported in similar groups of healthy men (15). In addition to a thinner arterial wall, our endurance-trained women had a larger femoral lumen diameter than sedentary women. The group differences in femoral diameter were even more dramatic when we normalized for total leg mass. Consistent with our earlier investigation in men (15), structural differences in the endurance-trained women were not related to basal femoral artery blood flow but were associated with a lower femoral shear stress and a higher mean tangential wall stress. These findings are consistent with the “expansive femoral artery remodeling” we reported recently in endurance-trained men (15), presumably due to the intermittent marked elevations in leg blood flow during training sessions and not under basal conditions. These presumed structural adaptations may have important physiological implications in that such remodeling is associated with a greater level of maximal aerobic capacity (44). Indeed, when ANCOVA was performed with maximal oxygen consumption as the covariate, the differences between endurance-trained and sedentary in femoral IMT and lumen diameter were no longer significant.

In the present study, the use of HRT regimens was associated with a smaller femoral IMT. This association persisted even after covarying for maximal oxygen consumption and other significant correlates of femoral

Table 4. Carotid artery characteristics in postmenopausal women by age and HRT status

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;65 Yr</th>
<th>≥65 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No HRT</td>
<td>HRT</td>
</tr>
<tr>
<td>Lumen diameter, mm</td>
<td>6.29 ± 0.10</td>
<td>6.11 ± 0.08†</td>
</tr>
<tr>
<td>IMT/lumen diameter</td>
<td>0.089 ± 0.003‡</td>
<td>0.093 ± 0.002‡</td>
</tr>
<tr>
<td>Shear stress, dyn/cm²</td>
<td>5.1 ± 0.2</td>
<td>5.7 ± 0.4</td>
</tr>
<tr>
<td>Tangential stress, 10³ dyn/cm²</td>
<td>6.5 ± 2.6</td>
<td>6.0 ± 1.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. <65 yr; †P < 0.05 vs. no HRT; ‡P < 0.05 vs. ≥65 yr no HRT.
IMT, thus demonstrating that the smaller IMT associated with HRT use is independent of influences of aerobic fitness and traditional atherosclerotic risk factors. In marked contrast to the associations we observed with endurance-training status, femoral artery diameter of HRT users was rather smaller than non-users. In addition, adjusting femoral IMT for differences in lumen diameter diminished the effect of HRT use to where it was no longer significant. We also found HRT use to be associated with a higher femoral artery shear stress but not with tangential wall stress, opposite to what we observed for endurance-trained associated effects. Collectively, these findings demonstrate intervention-specific differences in femoral artery remodeling between women who use HRT and those who participate in endurance-training activities.

As we observed for endurance training, no such favorable association with HRT use was evident in carotid IMT in the overall study population. The present findings differ from earlier investigations (19, 38, 42, 59) reporting that HRT use was related to a smaller carotid IMT. One possible explanation for this discrepancy could be because several of the previous studies (19, 38, 42) included smokers and women with CVD, whereas the present investigation included only nonsmoking healthy women free of overt chronic diseases. Indeed, the study by McGrath et al. (42) revealed that the association of HRT use with carotid IMT was only evident in smokers but not healthy nonsmokers. More specifically, the discrepancy may be related to the difference in the baseline IMT levels (with higher IMT to be affected to a greater extent). In the present study, when we selected a subgroup of older women ≥65 yr who had elevated IMT, carotid IMT was ~13% smaller in users compared with nonusers of HRT. This finding is consistent with the hypothesis that at least in healthy women, HRT may inhibit carotid hypertrophy primarily in the latter phase of the menopausal years (19, 42, 59). Moreover, carotid artery lumen diameter was smaller in the older subgroup of women who use HRT, suggesting that HRT use may also prevent the age-related increase in carotid artery dilation, which has recently been shown to be a risk factor independent of carotid IMT (32).

To our knowledge, the present study is the first to examine the association between combined HRT and endurance training status on vascular structure. Most of the available data on the interactive effects of combined HRT and habitual physical activity concern metabolism- and bone density-related effects in which combined HRT and exercise results in additive effects on both (7, 34). Although there were no statistically significant differences between endurance-trained users and nonusers and sedentary HRT users in the present study, postmenopausal women who participated in endurance-trained activities and who used HRT had the smallest mean IMT. Our findings support the use of a multifactorial risk intervention approach (49) and suggest that an additional benefit on IMT may be observed by practicing both lifestyle behaviors.

We can only speculate on the mechanisms for the site-specific effects of HRT and endurance training on IMT. One potential explanation is that the femoral artery is a predominantly muscular vessel whereas the carotid artery is elastic in nature (6). Muscular arteries have thicker medial layers and contain more smooth muscle cells compared with elastic arteries (53). Increases in IMT in healthy adults are thought to be due to smooth muscle cell hypertrophy within the medial layer (14), and, as such, muscular arteries may have more plasticity. In this context, HRT and regular exercise can influence several putative factors that are known to modulate smooth muscle cells in the arterial wall including sympathetic-adrenergic activity, circulating ANG II and endothelin-1, and locally released vasoactive factors such as nitric oxide (18, 20, 33, 39, 60). In the context of HRT, because estrogen inhibits smooth muscle cell hypertrophy through both estrogen receptor-dependent and -independent mechanisms, the site specificity we observed could be attributed to differences in vascular estrogen receptor expression or in the local metabolism of estradiol to catecholestrogens (16, 17, 62). In addition, HRT and habitual exercise may exert heterogeneous influences on the vessel wall of different arterial segments depending on variations in local metabolic requirements, hydrostatic pressures, and blood flow patterns, resulting in different mechanical and shear forces applied against the vessel wall (23). However, in the present study, carotid and femoral artery basal blood flows and shear stresses were not correlated with IMT.

There are at least five important limitations associated with the present study. First, because we only studied healthy nonsmoking postmenopausal women without evidence of overt chronic diseases, our results can only be generalized to this population of women. It is possible that HRT and/or habitual exercise could have beneficial effects on carotid IMT in postmenopausal women smokers and/or in women with chronic disease (i.e., atherosclerosis, diabetes, and hypertension). In this regard, however, recent findings (28, 30) from controlled clinical trials demonstrate no benefit of HRT on coronary heart disease in postmenopausal women with established coronary disease. These recent findings, along with an early report (30) of increases in early harm within the first year of HRT, cast doubt on the effectiveness of HRT for secondary prevention of coronary heart disease (45).

Second, because we used a cross-sectional study design, it is plausible that genetic or other constitutional factors may have influenced arterial IMT independent of HRT use and endurance-training status. However, we emphasize that the mean annual progression rate of carotid IMT for women aged 50–80 yr is reported to be very slow (0.015–0.02 mm/yr) (19). For the beneficial effects of HRT and habitual exercise to be manifest on carotid IMT, it may take years and such long-term intervention studies are difficult to complete. These observations may explain why recent randomized clinical trials have demonstrated no benefit of HRT on carotid IMT or other CVD outcome measures because
the trial durations have ranged between 2 and 4 yr (4, 28, 30). Indeed, there was a trend for late benefit at the end of 4 yr in the Heart Estrogen/Progestin Replacement Study (29). Third, Matthews et al. (41) reported that women using HRT are often healthier and more educated than nonusers. To eliminate such confounding factors as much as possible, within each habitual exercise group (sedentary or endurance trained) we matched users and nonusers of HRT for aerobic capacity, CVD risk factors, and socioeconomic status. Fourth, the inclusion of women using a variety of HRT regimens may have increased intersubject variability. For example, we were not able to account for the different modes of estrogen therapy (e.g., conjugated estrogens, oral, or transdermal estradiol) because of differences in estrogen replacement regimens. However, when we compared women who used unopposed estrogen with women who used a combination of estrogen and progesterin, we found no differences in IMT. Fifth, using high-resolution ultrasonography cannot discern between the intimal and the medial layers (51), and thus we cannot determine whether the smaller IMT associated with HRT and habitual exercise status are due to decreased intimal and/or medial thickening.

Our findings that the effects of HRT and habitual exercise are evident in muscular arteries may have important clinical implications. Increased IMT is associated with the risk of myocardial infarction stroke and occlusive peripheral artery disease and has demonstrated to be more powerful predictor of cardiovascular events in older adults than traditional risk factors (3, 46). Thickening of the arterial wall is thought to contribute to reduced arterial compliance and increased systemic and peripheral vascular resistance, which would increase the pulsatile afterload on the left ventricle, thereby increasing the risk for CVD (52). In addition, the lower IMT may buffer the adverse effects from which other CVD risk factors and comorbidities increase IMT to pathophysiological levels. Most of the studies performed to date have measured IMT in the carotid artery (3, 8, 46). Recent studies (37, 43) have demonstrated that femoral IMT may be a stronger predictor of coronary atherosclerosis than carotid IMT. Moreover, femoral IMT appears to be a more powerful predictor of CVD risk in women than in men (21). Although femoral arteries are perceived as more difficult to access and image, these previous studies together with our present results suggest the need to incorporate femoral artery imaging in clinical trials.

After menopause, women have a higher risk for CVD, presumably due to the loss of estrogen and/or reduced physical activity levels (5). As such, the smaller femoral IMT observed in postmenopausal women who use HRT and/or who perform habitual exercise may contribute to their reduced risk of CVD. Indeed, the 0.1 mm smaller IMT associated with both HRT and habitual exercise status would translate into a 10–20% reduction in risk for myocardial infarction (46). Moreover, HRT use is associated with other adverse effects, including an increased risk of breast cancer (11). However, despite the increased risk of breast cancer, the mortality rate among women taking HRT is lower because of the reduced number of deaths due to CVD and osteoporosis (12). Importantly, our findings indicate that regular exercise may be an alternative lifestyle intervention for women who cannot take HRT because of contraindications, side effects, or risk/fear of developing breast cancer. Indeed, habitual exercise has been associated with a reduced risk of CVD (10, 36, 40, 47). Perhaps combining both lifestyle behaviors may offset the adverse effects of HRT on breast cancer risk (8, 44). There are considerable data from observational studies demonstrating CVD protective effects with HRT use, as such, insight into the potential cardioprotective influences of HRT in healthy postmenopausal women remains an important issue.

In conclusion, the results of the present study indicate that HRT and endurance training are independently associated with femoral IMT in healthy postmenopausal women. Furthermore, HRT use is related to a smaller carotid IMT in older women. Thus a direct modulatory effect on arterial IMT may contribute, at least in part, to the reduced CVD risk in postmenopausal women who use HRT and/or perform regular aerobic exercise.

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