Age-Related Deterioration in Arterial Structure and Function in Postmenopausal Women
Impact of Hormone Replacement Therapy

Barry P. McGrath, Yu-Lu Liang, Helena Teede, Louise M. Shiel, James D. Cameron, Anthony Dart

Abstract—Epidemiological evidence suggests that hormone replacement therapy (HRT) reduces morbidity and mortality from cardiovascular diseases in postmenopausal women. In this study, indices of arterial function [total systemic arterial compliance (SAC) and carotid arterial distensibility coefficient (DC)], structure [carotid intima-media thickness (IMT)], and lipid profiles were compared in postmenopausal women on long-term HRT and aged-matched controls. One hundred nine women aged 44 to 77 years taking HRT and an age-matched group of 108 female controls were entered into the study. The two groups were similar for body mass index, smoking status, exercise level, alcohol intake, and blood pressure. Fasting cholesterol, low density lipoprotein, and lipoprotein(a) were reduced and high density lipoprotein increased in the HRT group. IMT increased with age; SAC and DC were reduced with age in both groups. The HRT group had a higher mean SAC (0.42±0.02 versus 0.34±0.02 U/mm Hg, \(P=0.0001\)) and a lower mean IMT (0.67±0.01 versus 0.74±0.02 mm, \(P=0.006\)) than did controls. Subgroup analysis for estrogen versus estrogen plus progestin revealed no differences for SAC and IMT; DC, however, was greater in estrogen-only users. Smokers on HRT had a higher mean SAC (0.41±0.02 versus 0.31±0.01 U/mm Hg, \(P=0.008\)) and a lower IMT (0.65±0.02 versus 0.75±0.03 mm, \(P=0.002\)) than did smokers not taking such therapy. A protective effect of long-term estrogen therapy on age-related changes in arterial structure and function in postmenopausal women was evident in smokers and nonsmokers alike. Progestin appeared to counteract the effects of estrogen on carotid compliance only. Long-term controlled trials are needed to determine the significance of these findings. (Arterioscler Thromb Vasc Biol. 1998;18:1149-1156.)

Key Words: arterial compliance ■ carotid intima-media thickness ■ estrogen ■ progestins ■ postmenopausal

A number of case-control, cohort, and cross-sectional studies have suggested that the potential beneficial effects of HRT in postmenopausal women for reducing the relative risk of cardiovascular disease are in the range of 40% to 50%.1–5 Results are still pending from long-term, prospective, controlled trials to substantiate a role for HRT in reducing cardiovascular morbidity and mortality in postmenopausal women. Many mechanisms have been proposed for estrogen’s effects on the rate of progression of atherosclerotic vascular disease.6–13 Estrogen therapy reduces LDL cholesterol and increases HDL cholesterol.5,7 It may also inhibit lipoprotein oxidation9 and inhibit proliferation of smooth muscle cells in arterial walls.9,10 Atherosclerotic plaque formation in arteries was reduced by estrogen therapy compared with placebo in cholesterol-fed rabbits11 and monkeys on a high-fat diet.12 Estrogen therapy alone or in combination with a progestin similarly limited atherosclerotic plaque development in experimental animals.13

Indices of arterial wall structure and function that can be measured by noninvasive techniques in humans include carotid wall IMT and arterial compliance. Arterial wall IMT is influenced by known cardiovascular risk factors14 and is a useful surrogate marker of coronary arterial disease.15 Arterial compliance is significantly correlated with factors known to affect the stiffness of arteries, such as age, hypertension, diabetes, and atherosclerotic vascular disease.16–22

In this study, we determined the indices of vascular function (systemic and carotid arterial compliance) and of vascular structure (carotid arterial IMT) in a large group of postmenopausal women receiving HRT for at least 1 year and in an aged-matched control group not on HRT. The impact of age on these vascular parameters and the effects of estrogen or estrogen plus progestin intervention on age-related changes in vascular health were studied.

Methods

Two hundred seventeen postmenopausal women were recruited for the study from an urban population in Melbourne, Australia. All subjects had been postmenopausal for at least 2 years. One hundred nine subjects were taking HRT, 57 on estrogen alone (primarily Premarin) and 52 on estrogen plus progestin therapy (primarily
Provera). An age-matched group of 108 women not on HRT was also studied. Each subject completed a questionnaire to assess cardiovascular risk factors based on the National Heart Foundation of Australia Risk Factor Prevalence study.27 The prevalence of smokers in the study (41%) was greater than that for women of equivalent age in the Australian community (22%), as a number of subjects who volunteered were participants in a separate study of male and female smokers at the study center.

The study protocol was approved by the Human Research and Ethics Committee, Monash Medical Center, Melbourne. Informed consent was obtained from all subjects. They were also advised not to take caffeine-containing drinks for at least 8 hours before vascular ultrasound measurements, which were performed in a quiet, air-conditioned clinical laboratory after the subjects had been resting in the supine position for at least 10 minutes. Serum samples for lipid profile analysis were collected after an 8-hour fast.

Total SAC
In all 217 subjects, as depicted in Figure 1, SAC was estimated by the “area method,” which requires measurement of volumetric blood flow and associated driving pressure to derive an estimated compliance over the total systemic arterial tree.17,24 A 3.5-MHz continuous-wave Doppler flow velocimeter (Multidoplex MD1, Huntleigh Technology) was placed on the suprasternal notch to estimate ascending aortic blood flow. Aortic driving pressure was estimated by application tonometry of the carotid artery by using a noninvasive pressure transducer (Millar Mikro-tip, Millar Instruments). The pressures obtained by this method were calibrated against brachial artery pressure measurements by using a Dinamap device (CRITIKON 1846 SX).

The formulas used for calculation of SAC were as follows:

\[
SAC = \frac{A_d}{R(P_s-P_d)}
\]

\[
R = \frac{MAP}{Q_{mean}}
\]

\[
Q_{mean} = \frac{MAP}{\pi r^2 \times F_{mean}}
\]

\[
r = 0.25 \times BSA + 0.52
\]

\[
BSA = \frac{0.425 \times \text{Weight (kg)} \times 0.725 \times \text{Height (cm)} \times 71.44}{10000}
\]

where \(A_d\) is the area under the BP-diastolic decay curve from end-systole to end-diastole; \(P_s\) is end-systolic BP (carotid); \(P_d\) is end-diastolic BP (carotid); \(MAP\) is mean arterial pressure; \(R\) is total peripheral resistance; \(Q_{mean}\) is mean flow; \(F_{mean}\) is mean velocity; \(r\) is aortic root radius; and \(BSA\) is body surface area.

The formula for estimation of \(r\) from \(BSA\) was based on the work of Roman et al.29 and data from our own laboratory. In all subjects enrolled in this study, calculated SAC values were derived from estimated aortic root diameter (\(SAC_{\text{echo}}\)). These were compared with \(SAC_{\text{echo}}\) an alternative methodology based on echocardiographic assessment of the aortic root diameter. There was very close agreement between \(SAC_{\text{echo}}\) and \(SAC_{\text{BSA}}\) (\(r=0.91, n=56, P<0.001\)). A Bland-Altman plot28 showed no significant trend with increasing SAC.

Repeatability of the SAC measurements was assessed in a subgroup of the study population. Twenty-eight subjects attended the study center on 2 separate occasions 2 to 4 weeks apart without changing any therapy or lifestyle features over the interval. The correlation coefficient for SAC between the 2 visits was 0.74; the coefficient of variation was 11.2%; the mean difference±SD was 0.05±0.14 U/mm Hg; and the coefficient of repeatability was 0.28. These results are similar to those previously reported using the same technique.27 Kupari and colleagues.18 used magnetic resonance techniques to assess the elastic modulus of the ascending aorta, with a repeatability of ~20%.

Ultrasound Imaging
One hundred fifty-five subjects, 78 on HRT and 77 not on HRT, were further investigated with lipid profiles and an imaging study of the common carotid arteries. This was performed by using a high-resolution ultrasound machine (Diasonics DRF-400) with a 7.5-MHz mechanical sector transducer (7.5-SPC). A region 1 cm proximal to the origin of the bulb of the right common carotid artery was identified by B-mode ultrasonography. Of all sites that have been used in ultrasound studies for the assessment of IMT, this region has been demonstrated to provide the most reproducible results when measurements are performed in more than 1 direction.28 The transducer was manipulated so that the near wall of the carotid artery was parallel to the transducer footprint and the lumen was maximized in the longitudinal plane for both B-mode imaging and M-mode recording. Three images of each B-mode, taken from different angles (anterior, anterolateral, and lateral), and 5 images of each M-mode were recorded. The images were digitized and saved on computer via a customized computer program using A House of Windows software (C. Smith, Auckland, New Zealand) as previously described.27 Brachial BP recordings were taken at 5-minute intervals throughout the period of ultrasound imaging by using a Dinamap device (CRITIKON 1846 SX).

Image Analysis
A B-mode scan of an artery is characterized by two echogenic lines (known as leading edges) separated by a hypoechoic space. Based on the work of Pignoli and colleagues,30 it has become accepted, though not without challenge,31 that the outer line corresponds anatomically to the media-adventitia interface. It is generally agreed that the inner line corresponds to the lumen-intima interface. The distance between the two lines thus represents the IMT. The results for IMT and carotid diameter changes for assessing carotid compliance were analyzed by using the customized A House of Windows software program as previously reported.29 Each image

Selected Abbreviations and Acronyms

- BMI = body mass index
- BP = blood pressure
- DC = distensibility coefficient
- HRT = hormone replacement therapy
- IMT = intima-media thickness
- SAC = systemic arterial compliance

Figure 1. Measurement of systemic arterial compliance by the area method is derived from the carotid BP waveform and aortic root blood flow. This figure shows a carotid pressure profile obtained by applanation tonometry. \(A_d\) is area under the diastolic portion of the pulse pressure contour, \(P_s\) is end-systolic arterial BP, and \(P_d\) is end-diastolic arterial BP.
was recalled (magnification ×5), and the distance between two successive R waves was determined from the ECG tracing. A 1-cm longitudinal section of the image of the common carotid artery was divided into 10 equal segments by using a computer-generated grid, and the investigator was able to select media-adventitia and lumen-intima interfaces for the near and far walls of the carotid artery by positioning a cursor at each intersection where a grid line crossed the vessel wall. The cursor could move freely in the vertical but not in any other direction. Measurements were automatically transferred and saved in a database (Quest for Windows, version 2.1). Only the IMT measurements for the far wall of the right common carotid artery were used for the data analysis in this study.

Two parameters were estimated: (1) right common carotid arterial far-wall IMT and (2) the DC, a measure of the change in carotid artery cross-sectional area for a change in BP relative to its initial cross-sectional area.

The formula for calculation of carotid compliance was as follows:

\[
DC = \frac{\Delta A}{D^2 \Delta P}
\]

where \(A\) is cross-sectional area; \(\Delta D\) is change in diameter of the distal common carotid artery; \(D\) is diastolic diameter; and \(\Delta P\) is the difference between average systolic and average diastolic BP. Carotid BP was the carotid pressure waveform obtained by applanation tonometry and scaled by linear interpolation from measured mean end-diastolic BP.21

The repeatability of these measurements was assessed in a subgroup of the study population. A single investigator (L.M.S.) performed all IMT and carotid wall compliance measurements. Twenty-nine subjects attended the study center on 2 separate occasions 2 to 4 weeks apart, without having changed any therapy or lifestyle features over the interval. The correlation coefficient for IMT between the 2 visits was 0.92; the coefficient of variation was 5.6%; the mean difference ± SD was 0.03 ± 0.01 mm; and the coefficient of repeatability was 0.02. A Bland-Altman plot26 showed no significant trend with increasing IMT.

Lipid Measurements

Fasting venous blood samples for total cholesterol and triglyceride measurements were collected from all 155 subjects who underwent both SAC and carotid imaging studies. Fifty percent of these subjects were randomly selected for additional fasting HDL cholesterol, LDL cholesterol, and Lp(a) measurements.

Statistical Analysis

Student’s unpaired \(t\) test was used to compare differences in mean values for group characteristics, lipids, arterial compliance, and carotid IMT measurements for HRT and non-HRT groups. All measurements except those for Lp(a) were normally distributed. Differences between groups for Lp(a) were assessed by nonparametric statistical methods. Two subgroup analyses were performed: (1) subjects who were being treated with estrogen alone versus those who were being treated with estrogen plus progestin and (2) smokers versus nonsmokers. Linear regression analysis was used to examine the relationships between indices of arterial compliance, IMT, and age. A multiple linear regression model was developed to analyze relationships between HRT, cardiovascular risk factors, and vascular parameters. ANOVA and ANCOVA were used to adjust for interactions between variables. Data are given as mean±SEM.

Results

The HRT and non-HRT groups were not significantly different for weight, height, BMI, smoking status, BP, alcohol intake, and exercise (Table 1). Ten subjects in each group were on antihypertensive medications. Four subjects in the non-HRT group had mean BP readings >160 mm Hg systolic or 90 mm Hg diastolic after 3 readings at rest. In the subgroup analysis smokers were slightly but significantly older than nonsmokers, with the groups otherwise well matched (Table 2). Duration of therapy was similar in the estrogen and combined-therapy groups (88 ± 10 versus 70 ± 7 months, \(P=NS\)), as it was in the smokers compared with nonsmokers (79 ± 11 versus 80 ± 2 months, \(P=NS\)).

The results for the plasma lipids in the HRT and control groups are shown in Figure 2. Mean plasma total and LDL cholesterol were significantly lower and mean HDL cholesterol significantly increased in the HRT group compared with controls. Mean values for triglyceride were not significantly different in the two groups. Lp(a) analyzed by nonparametric measures was lower in the HRT group (202 ± 39 versus 357 ± 58 mg/L, \(P=0.04\)). Smokers had higher total cholesterol and triglyceride levels than did nonsmokers (Table 2).

Arterial Compliance: SAC

Comparisons of mean values for indices of arterial compliance are summarized in Table 3. Mean SAC was significantly greater in the HRT group compared with the non-HRT group (0.42 ± 0.02 versus 0.34 ± 0.02 U/mm Hg, \(P=0.003\)). For the HRT group, there was no significant difference in SAC for smokers versus nonsmokers (Table 2).

### Table 1. Characteristics of the Study Population: Control vs HRT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n=108)</th>
<th>HRT (n=109)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.4±0.7</td>
<td>59.7±0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.61±0.006</td>
<td>1.61±0.005</td>
<td>0.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.3±1.3</td>
<td>67.1±1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.8±0.5</td>
<td>25.6±0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>50 (46%)</td>
<td>39 (36%)</td>
<td>(\ldots)</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>69±0.9</td>
<td>71±0.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>93±1</td>
<td>92±1</td>
<td>0.5</td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>123±2.7</td>
<td>122±2.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>82±2.3</td>
<td>81±2.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Alcohol, drinks/d</td>
<td>0.6±0.1</td>
<td>0.6±0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Exercise, h/wk</td>
<td>2.7±0.4</td>
<td>2.1±0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Results are presented as mean±SEM. Controls are postmenopausal women not on HRT. HRT are postmenopausal women on HRT.*

### Table 2. Characteristics of the Study Population: Smokers vs Nonsmokers

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Smokers (n=89)</th>
<th>Nonsmokers (n=128)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, m</td>
<td>1.62±0.005</td>
<td>1.62±0.005</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.6±1.3</td>
<td>66.7±0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6±0.5</td>
<td>25.8±0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>HRT, n (%)</td>
<td>39 (%)</td>
<td>69 (%)</td>
<td>(\ldots)</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>94±1</td>
<td>92±1</td>
<td>0.09</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±0.7</td>
<td>59±0.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Total chol, mmol/L</td>
<td>6.4±0.2</td>
<td>5.8±0.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.7±0.1</td>
<td>1.3±0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.8±0.1</td>
<td>3.7±0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.6±0.5</td>
<td>1.7±0.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Chol indicates cholesterol. Results are presented as mean±SEM.*
those receiving combined estrogen and progestin therapy compared with those on estrogen alone (Table 3). Comparisons of smokers with nonsmokers are shown in Table 4. Smokers on HRT had a higher mean SAC than did smokers in the control group (0.41±0.02 versus 0.31±0.02 U/mm Hg, P=0.008). There was no significant difference between smokers on HRT and control nonsmoking subjects (0.41±0.02 versus 0.35±0.03 U/mm Hg, P=NS).

The best predictive multiple linear regression model was developed by incorporating systolic and diastolic BPs, pulse pressure, smoking status, cholesterol, triglycerides, BMI, heart rate, and alcohol intake status of all subjects. SAC correlated best with HRT status (P<0.0001, r=0.55). BMI (P=0.002), triglycerides (P=0.003), alcohol intake (P=0.02), and smoking status (P=0.04) were the only other significant correlates in the model. ANCOVA with BMI, triglycerides, alcohol intake, smoking status, and BP as covariates demonstrated that SAC was still significantly correlated with HRT status.

SAC decreased with age in both HRT and control groups. There was no significant difference in the slope of the linear SAC-age relationship between the HRT and control groups (Figure 3). However, at any given age, the HRT group had a more favorable SAC than did controls, as represented by a significant upward shift in the SAC-age relationship. There was no correlation between duration of HRT use and SAC.

**Carotid Compliance**

Mean DC was not significantly different between the HRT and non-HRT groups (Table 3). However, comparison of estrogen-alone with estrogen-plus-progestin treatment subgroups showed significant differences in mean DC, consistent with a greater degree of arterial stiffness in the combined-therapy HRT group compared with those on estrogen alone. In the smoking subgroup analysis DC was higher in smokers on HRT (44±4×10⁻³ versus 36±2×10⁻³/kPa, P=0.06) compared with smokers in the control group. In nonsmokers mean DC was not significantly different in the HRT and control groups (Table 4).

The best predictive multiple linear regression model, based on BP, age, HDL, LDL, triglycerides, smoking status, and HRT status of all subjects, demonstrated that DC was significantly correlated only with systolic BP (P<0.001).

**Common Carotid Wall IMT**

Mean arterial carotid wall IMT was 0.67±0.01 mm in the HRT group compared with 0.74±0.02 mm in controls (P<0.006). The mean IMT values for estrogen-treated and combined estrogen and progestin–treated subgroups were not significantly different (Table 3). Overall IMT was not significantly different in smokers compared with nonsmokers (0.71±0.02 versus 0.69±0.02 mm); however, smokers on HRT had a significantly lower IMT than did smokers not on HRT (0.65±0.01 versus 0.75±0.01 mm, P=0.002) (Table 4).

There was a significant increase in IMT with age in both HRT and non-HRT groups. This IMT-age correlation was stronger in the control group (r=0.51, P<0.001) compared with the HRT group (r=0.32, P=0.04), with the difference between linear regression lines slopes approaching significance (P=0.08) (Figure 4). In subjects ≤60 years of age IMT was not significantly different in those on HRT compared with controls (0.63±0.02 versus 0.66±0.02 mm, P=NS). In subjects >60 years of age, those who were on HRT had a significantly lower mean IMT (0.70±0.02 versus 0.80±0.03 mm, P=0.01).

The best predictive multiple linear regression model for IMT was based on systolic and diastolic BPs, HRT status, age, alcohol intake, and activity levels of all subjects. IMT was significantly correlated with HRT status (P=0.002), systolic BP (P<0.0001), diastolic BP (P=0.004), and age (P=0.007). IMT was not significantly correlated with lipid levels. ANCOVA with BP and age as covariates demonstrated that IMT was still independently correlated with HRT status.

**Relationships Between Arterial Compliance and Wall Thickness**

Linear regression analyses (Table 5) showed no significant relationship between SAC and IMT for the HRT group (r=−0.13, P=0.3) but a significant inverse correlation for

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**Table 3. Carotid IMT, SAC, and DC Measurements: Control vs HRT Groups and Subgroups of HRT**

<table>
<thead>
<tr>
<th></th>
<th>Non-HRT</th>
<th>HRT Total</th>
<th>P</th>
<th>Est</th>
<th>Est+Prog</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid IMT, mm</td>
<td>0.74±0.02</td>
<td>0.67±0.01</td>
<td>0.006</td>
<td>0.67±0.01</td>
<td>0.66±0.02</td>
<td>0.8</td>
</tr>
<tr>
<td>(n=77)</td>
<td>(n=79)</td>
<td>(n=45)</td>
<td></td>
<td>(n=34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic compliance (SAC), U/mm Hg</td>
<td>0.34±0.02</td>
<td>0.42±0.02</td>
<td>0.003</td>
<td>0.43±0.02</td>
<td>0.42±0.02</td>
<td>0.2</td>
</tr>
<tr>
<td>(n=108)</td>
<td>(n=107)</td>
<td>(n=56)</td>
<td></td>
<td>(n=51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid compliance (DC), ×10⁻³/kPa</td>
<td>39±2</td>
<td>42±2</td>
<td>0.5</td>
<td>47±3</td>
<td>35±3</td>
<td>0.005</td>
</tr>
<tr>
<td>(n=77)</td>
<td>(n=78)</td>
<td>(n=44)</td>
<td></td>
<td>(n=34)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Est indicates women on estrogen alone; Est+Prog, women on combined estrogen plus progesterone therapy. Controls were postmenopausal women not on HRT. Results are presented as mean±SEM.
the control group ($r = -0.31, P = 0.006$). DC was significantly correlated with SAC in both HRT ($r = 0.40, P < 0.001$) and control ($r = 0.38, P = 0.001$) groups. DC was inversely correlated with IMT in both HRT ($r = -0.28, P = 0.01$) and control ($r = -0.35, P = 0.001$) groups.

### Discussion

Epidemiological evidence has strongly suggested that HRT may reduce the risk of cardiovascular disease in postmenopausal women.1,4,5,32,33 The results of long-term controlled trials such as the Women’s Health Initiative study are not expected until early in the next century. Potential mechanisms for the effects of HRT on cardiovascular disease include alterations in plasma lipoproteins and lipid oxidation.5,7,8 These effects are estimated to account for 40% to 50% of the beneficial estrogen effect. Changes in the coagulation pathways including fibrinogen,34 modulation of the levels or effects of vasoactive hormones,6,35 and changes in arterial wall structure10,36 and function37–42 have also been identified. The results of the present study offer strong supporting evidence that long-term estrogen therapy in postmenopausal women can beneficially affect arterial structure and function.

Indices of arterial structure and function can be measured accurately, reproducibly, and noninvasively by ultrasound. These measurements are well suited to clinical intervention trials to study surrogate clinical end points. IMT, as assessed by B-mode ultrasound imaging, provides an index of carotid wall structure and appears to be a useful marker of atherosclerosis. It is believed to measure the combined thickness of the intima and media,30 although Gamble et al31 reported that the measurement best represents total wall thickness. IMT has been correlated with the majority of cardiovascular risk factors, including age, male sex, hypertension, hypercholesterolemia, diabetes, and pack-years of smoking14 and also with the extent of coronary disease.15 IMT can also be influenced by antihypertensive43,44 and lipid-lowering45,46 therapy. In the present study IMT was significantly reduced by a mean value of 0.07 mm in the group of women on HRT compared with the age-matched control group. In the entire group of subjects, the multiple regression model revealed that IMT was significantly correlated with HRT status, age, and systolic and diastolic BP. IMT remained significantly correlated with HRT status after correction for age and BP. These results support the findings of the Asymptomatic Carotid Atherosclerosis Progression Study (ACAPS) investigators.36 Thus, HRT appears to produce changes in vessel wall structure over the long term, and this may be an important mechanism by which HRT exerts its cardiovascular protective effect. The mechanisms mediating HRT effects on arterial structure in postmenopausal women are not yet

### Table 4. Compliance and IMT Measurements: Smokers vs Nonsmokers ± HRT

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>HRT</th>
<th>$P$</th>
<th>Nonsmokers</th>
<th>HRT</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid IMT, mm (n=50) (n=39)</td>
<td>0.75±0.01</td>
<td>0.65±0.01</td>
<td>0.002</td>
<td>0.70±0.03</td>
<td>0.68±0.01</td>
<td>0.7</td>
</tr>
<tr>
<td>Systemic compliance (SAC), U/mm Hg (n=50) (n=38)</td>
<td>0.31±0.02</td>
<td>0.41±0.02</td>
<td>0.008</td>
<td>0.35±0.03</td>
<td>0.43±0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Carotid compliance (DC), $\times 10^{-3}$/kPa (n=50) (n=39)</td>
<td>36±2</td>
<td>44±4</td>
<td>0.06</td>
<td>45±3</td>
<td>39±0.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Controls were postmenopausal women not on HRT. Results are presented as mean±SEM.
TABLE 5.  Multiple Regression Analysis on the Interaction Between Vascular Parameters

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Numbers</td>
<td>r</td>
</tr>
<tr>
<td>IMT vs age</td>
<td>79</td>
<td>0.32</td>
</tr>
<tr>
<td>SAC vs age</td>
<td>107</td>
<td>−0.22</td>
</tr>
<tr>
<td>DC vs age</td>
<td>78</td>
<td>−0.35</td>
</tr>
<tr>
<td>SAC vs IMT</td>
<td>79</td>
<td>−0.13</td>
</tr>
<tr>
<td>SAC vs DC</td>
<td>78</td>
<td>0.4</td>
</tr>
<tr>
<td>DC vs IMT</td>
<td>78</td>
<td>−0.28</td>
</tr>
</tbody>
</table>

Results are presented as correlation coefficients.

clarified. IMT may be influenced by lipid profile changes, but on available evidence, this is likely to account for only some of the variations between HRT and controls. Lipids were not correlated with IMT in this study.

SAC and common carotid compliance provide noninvasive measures of arterial function. They have been less studied when compared with IMT but are also affected by cardiovascular risk factors. SAC reflects the function of the proximal vascular system to convert pulsatile, systolic blood flow into continuous blood flow to the periphery. It is inversely proportional to arterial stiffness. In this study, mean SAC was higher in the HRT group and similar for combined HRT and estrogen-alone subgroups. These observations could not be explained by any differences between groups for weight, BMI, smoking status, alcohol intake, exercise levels. The HRT group had significantly lower total plasma cholesterol, LDL, and Lp(a) levels and higher HDL cholesterol levels. Thus, arterial compliance in the HRT group may have been influenced by changes in the vascular wall mediated by HRT-induced changes in plasma lipids or lipoprotein oxidation. This is unlikely to be the only mechanism, because SAC was not significantly correlated with lipid levels (except for triglycerides) in either the HRT or control group. SAC was higher in the HRT group and similar for combined HRT and estrogen-alone subgroups. These observations could not be explained by any differences between groups for weight, BMI, smoking status, alcohol intake, exercise levels. The HRT group had significantly lower total plasma cholesterol, LDL, and Lp(a) levels and higher HDL cholesterol levels. Thus, arterial compliance in the HRT group may have been influenced by changes in the vascular wall mediated by HRT-induced changes in plasma lipids or lipoprotein oxidation. This is unlikely to be the only mechanism, because SAC was not significantly correlated with lipid levels (except for triglycerides) in either the HRT or control group. SAC was higher in the HRT group and similar for combined HRT and estrogen-alone subgroups. 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important role in cardiovascular protection. Interestingly, in the current study the duration of HRT use was not associated with IMT even after correction for age. In the ACAPS\(^5\) and ARIC\(^6\) studies the reported annual rates of progression of mean maximal carotid IMT for women aged 50 to 80 years were 0.015 to 0.02 mm per year. In a preliminary report from ACAPS, Espeland et al\(^6\) reported that HRT may reduce or halt progression of IMT. Our results are in agreement with theirs, since we observed a significantly lower mean IMT in the HRT group compared with the control group. Moreover, the IMT-age relationship appeared to be influenced by HRT, with the disparity between controls and those on HRT increasing with age, because the observed effects of HRT were more marked in older participants (Figure 4). This effect appears to be estrogen mediated because it is apparently not compromised by concomitant progestin therapy. The difference in IMT between the control and HRT groups was 0.07 mm, consistent with at least a 4- to 5-year protective benefit of HRT. Vascular function also deteriorates with age. Celemajer et al\(^40\) reported an age-related reduction in flow-mediated arterial dilatation, consistent with attenuation of NO-mediated responsiveness. Our results show that arterial function (ie, SAC and DC) deteriorated with age in postmenopausal women. As previously discussed, functional changes have been demonstrated to occur in the short term in response to intervention with HRT.\(^{41,42}\) The observation that HRT shifts the linear SAC-age relationship upward (Figure 3) is consistent with these studies.

Overall, the findings of this cross-sectional study in a large group of women suggest an apparent protective effect of long-term estrogen therapy on age-related changes in arterial function and structure after menopause. These effects were evident in smokers and nonsmokers alike, with smokers on HRT having vascular indices that were similar to those of nonsmokers not on HRT. The HRT group exhibited the expected beneficial effects of therapy on plasma lipids; however, HRT status was a significant correlate of SAC and IMT after adjustment for lipid profiles. Long-term controlled trials are needed to further examine the impact of estrogen therapy on arterial structure and function in postmenopausal women and their relationship to cardiovascular end points.

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References


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