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Hormone Replacement Therapy in Postmenopausal Women Protects Against Smoking-Induced Changes in Vascular Structure and Function

Helena J. Teede, MBBS,* Yu-Lu Liang, MB,* Louise M. Shiel, BSc,* John J. McNeil, MBBS, PhD,† Barry P. McGrath, MBBS, MD*

Clayton and Melbourne, Australia

OBJECTIVES The purpose of this study was to investigate the role of hormone replacement therapy (HRT) in postmenopausal women who smoke.

BACKGROUND Hormone replacement therapy appears to afford cardiovascular protection in postmenopausal women; however, in high risk individuals, specifically smokers, this has not been adequately studied. This question was addressed in a cross-sectional study of arterial structure, function and plasma lipids in postmenopausal smokers and nonsmokers.

METHODS Vascular ultrasound was performed in two age-matched groups of postmenopausal women, 70 on HRT (35 smokers) and 70 control subjects not on HRT (35 smokers). Indexes of arterial structure (carotid intima–media thickness [IMT]) and vascular function (systemic arterial compliance [SAC]) and lipid profiles were measured.

RESULTS Participant characteristics were similar in the two groups. Smokers on HRT, compared with smoking control subjects, had lower cholesterol (6.0 ± 0.2 vs. 6.8 ± 0.3 mmol/liter, $p = 0.03$) and more favorable mean values for IMT (0.64 ± 0.02 vs. 0.74 ± 0.03 mm, $p = 0.007$) and SAC (0.41 ± 0.03 vs. 0.32 ± 0.03 U/mm Hg, $p = 0.03$). Nonsmokers on HRT compared with nonsmoking control subjects had lower total cholesterol (5.7 ± 0.2 vs. 6.5 ± 0.2 mmol/liter, $p = 0.02$) and low density lipoprotein cholesterol (3.4 ± 0.2 vs. 4.4 ± 0.3 mmol/liter, $p = 0.01$). Mean IMT and SAC values in nonsmokers on HRT and control subjects were not significantly different. Multiple regression demonstrated significant correlation between HRT status and both IMT and SAC, in smokers and in those with increased cholesterol. In nonsmokers and those with lower cholesterol, HRT status was not significantly correlated with vascular parameters.

CONCLUSIONS In postmenopausal women who smoke there may be a beneficial effect of long-term estrogen therapy on indexes of arterial structure and function as surrogate markers of cardiovascular disease. Long-term controlled studies are needed to confirm these findings. (J Am Coll Cardiol 1999;34:131–7) © 1999 by the American College of Cardiology

Vascular disease is the leading cause of death among postmenopausal women in the western world. There have been 75 original observational and epidemiologic studies published on prevention of ischemic heart disease by hormone replacement therapy (HRT). This evidence supports a 40% to 50% reduction in the relative risk of cardiovascular disease in postmenopausal women on HRT (1–3).

The proposed mechanisms of estrogen action on atherosclerotic vascular disease and on vascular structure and function are diverse (4–6). Estrogen improves lipid profiles, with higher high density lipoprotein (HDL) and lower total and low density lipoprotein (LDL) cholesterol (7) and

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inhibits lipoprotein oxidation (8). In animal models estrogen reduces coronary intimal plaque development (9) and inhibits proliferation of vascular smooth muscle cells (10). Beneficial changes in carbohydrate metabolism, body fat distribution (7), fibrinolysis and coagulation profiles (11,12) have been noted. Endothelial function mediated by nitric

From the *Department of Medicine, Monash University, Monash Medical Centre, Clayton, Victoria, Australia; and †Department of Epidemiology and Preventative Medicine, Monash University, Alfred Hospital, Melbourne, Victoria, Australia. This study was supported by a Grant-in-Aid from the National Heart Foundation of Australia G95M4418 and a Grant from the NH&MRC 930409.

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Abbreviations and Acronyms

ANOVA = analysis of variance
HDL = high density lipoprotein
HRT = hormone replacement therapy
IMT = intima–media thickness
LDL = low density lipoprotein
SAC = systemic arterial compliance

oxide is also improved by estrogen (5). Impaired endothelial function has been demonstrated in smokers, along with altered lipid oxidation and increased atherosclerosis (8,13) contributing to an increased risk of cardiovascular disease. Potentially estrogen therapy may reduce cardiovascular risk in postmenopausal smokers through these and other mechanisms.

The role of estrogen therapy in cardiovascular protection in smokers is unclear. No specific observational or interventional trials have focused on the role of HRT in smokers. Several observational studies on cardiovascular protection and HRT have performed subgroup analyses in smokers with conflicting results; however, most have had inadequate sample sizes to address the issue (1,2). The results of long-term, prospective controlled trials are underway, with the projected statistical power to confirm the cardiovascular protective effect of HRT in postmenopausal women. To date the only controlled interventional trial completed is the Heart and Estrogen/Progestin Replacement Study (HERS) (14), a secondary prevention study in older women with established vascular disease treated with combined continuous medroxyprogesterone acetate with conjugated equine estrogen. This and other ongoing controlled trials do not analyze specific high risk subgroups including smokers, with specific intervention studies in smokers unlikely to be feasible given the costs involved and numbers required.

As an alternative to large-scale intervention trials based on clinical end points, noninvasive surrogate markers of vascular disease have been developed as intermediate end points. The early phase of atherosclerosis can be studied using carotid artery intima–media thickness (IMT), a measure of vascular structure. In large population studies IMT was significantly correlated with all the major cardiovascular risk factors (15–17) and was shown to be a useful surrogate marker of coronary arterial disease (17). Prospective studies have shown that IMT increases with age (15), yet women on HRT exhibit blunted age-related changes in IMT (18). Systemic arterial compliance (SAC), a measure of central conduit artery mechanical properties, reflects the ability of the proximal vascular system to convert pulsatile ventricular flow into smooth continuous peripheral blood flow. Systemic arterial compliance is related to the elasticity of the vessels and is influenced by age, hypertension, atherosclerotic vascular disease, exercise training and lipid-lowering and antihypertensive drugs (19–22). Hormone replacement therapy has been demonstrated to significantly improve arterial compliance in the short term (4).

In this study we have measured plasma lipids, IMT and SAC in a large group of postmenopausal women on HRT and an age-matched control group. We specifically sought to determine whether HRT had protective vascular benefits in smokers, with half of the population in each group being smokers.

METHODS

Postmenopausal women were recruited by advertisement from an urban population in Melbourne, Australia. Participants were studied as a baseline assessment before enrollment in an interventional study focusing on the use of antioxidants in the prevention of cardiovascular disease. One hundred and forty consecutive subjects were selected based on HRT and smoking status with inclusion of age-matched controls. All subjects were postmenopausal for at least two years with the HRT group being current users on therapy for at least one year. Seventy smokers (35 on HRT and 35 control subjects) were compared with 70 nonsmokers (35 on HRT and 35 control subjects). Smokers were defined as current smokers of a minimum of five cigarettes per day with an average smoking history of 38.3 pack years. The primary estrogen used was conjugated equine estrogen (Premarin) and the progestin was medroxyprogesterone acetate (Provera). Forty-one were on estrogen alone; 29 were on combined estrogen and progestin therapy. Subjects were healthy as assessed from history questionnaire (those with a history of osteoporosis were not excluded) and no participants had uncontrolled hypertension. A questionnaire based on the National Heart Foundation of Australia Risk Factor Prevalence study was completed by each participant to assess cardiovascular risk factors (23). Vascular parameters were ascertained in all participants; fasting total LDL and HDL cholesterol and triglycerides were measured in 100 participants. Height, weight and heart rate were determined and multiple blood pressure readings obtained in all participants.

The Human Research and Ethics Committee, Southern Health Care Network, Melbourne approved the study protocol. Informed consent was obtained from all subjects. Participants were advised against consuming caffeine-containing drinks for 8-h before ultrasound measurements, which were performed in a quiet air-conditioned clinical laboratory after subjects had been resting in the supine position for at least 10 min. Serum samples for lipid profile analyses were collected after an 8-h fast.

Vascular Parameters

Intima–media thickness. This parameter was derived from noninvasive ultrasound of the common carotid arteries, using a high resolution ultrasound machine (Diasonics DRF-400, Milipitas, California) with 7.5-MHz mechanical sector transducer (7.5-SPC). The IMT was defined as the distance

Table 1. Characteristics of the Study Population: HRT Versus Control Subjects in the Overall Study Population and in Smokers and in Nonsmokers

	All Subjects			Smokers			Nonsmokers		
Characteristics	HRT	Controls	p Value	HRT	Controls	p Value	HRT	Controls	p Value
Age (yr)	60 ± 1	60 ± 1	0.8	60 ± 1	60 ± 1	0.9	60 ± 1	60 ± 1	0.8
Height (m)	1.62 ± 0.01	1.61 ± 0.01	0.3	1.62 ± 0.01	1.62 ± 0.01	0.9	1.62 ± 0.01	1.60 ± 0.01	0.2
Weight (kg)	67 ± 1	68 ± 2	0.4	66 ± 2	68 ± 2	0.4	67 ± 2	68 ± 2	0.7
BMI (kg/m^2)	25 ± 0.4	27 ± 0.6	0.1	25 ± 0.6	27 ± 1	0.2	26 ± 0.6	27 ± 0.8	0.3
Systolic BP (mm Hg)	134 ± 2	134 ± 2	1	134 ± 3	135 ± 3	0.9	134 ± 4	134 ± 4	0.9
Diastolic BP (mm Hg)	74 ± 1	74 ± 1	0.7	74 ± 1	74 ± 2	0.9	74 ± 2	75 ± 1	0.6
Mean BP (mm Hg)	94 ± 1	94 ± 1	0.9	94 ± 2	94 ± 2	0.9	94 ± 2	92 ± 2	0.7

Results are presented as mean ± SEM.
BMI = body mass index; BP = blood pressure; HRT = hormone replacement therapy.

between the blood–intima and media–adventitia boundaries on B-mode imaging (24). The far wall of the right common carotid artery 1 cm proximal to the origin of the bulb was selected, as it has been shown to be the most reproducible (25). Three B-mode images were recorded from different angles, then digitized and saved on computer via a customized computer program using "A House of Windows" software (C. Smith, Auckland, New Zealand) as previously described (26). Brachial blood pressure recordings were recorded at 5-min intervals throughout the imaging period using a Dinamap device (Critikon, 1846 SX, Tampa, Florida). Image analysis was performed using a standardized measurement protocol, using 30 data points per subject, by the same sonographer (18). Measurements were automatically transferred and saved in a database (Quest for Windows, version 2.1, Gupta Corp.).

Total systemic arterial compliance. Assessment of SAC was based on the classical two-element Windkessel model and the "area method" calculation of Liu et al. (27). Noninvasive determination of blood flow using Doppler techniques and pressure waveforms obtained with applanation tonometry were applied to determine SAC as previously described (18,22,27). Aortic volumetric blood flow was measured from a handheld 3.5-MHz continuous wave Doppler flow velocimeter (Multidoplex MD1, Huntleigh Technology, Cardiff, U.K.) at the suprasternal notch. Simultaneous carotid driving pressure was ascertained by applanation tonometry with a pressure transducer (Millar Mikro-tip, Millar Instruments, Houston, Texas) over the carotid artery, with pressures calibrated against Dinamap brachial artery pressure measurements (Critikon 1846 SX).

The following formula was used to calculate compliance over the total systemic arterial tree (22,27): SAC = Ad/R(Ps − Pd), where Ad = area under the blood pressure diastolic decay curve from end-systole to end-diastole; Ps = end-systolic blood pressure (carotid); Pd = end-diastolic blood pressure (carotid); and R = total peripheral resistance derived from blood pressure and aortic root blood flow measurements.

A recent repeatability study was completed in 50 adult participants who attended twice in one month with no change in therapy or lifestyle. Bland-Altman plots showed satisfactory repeatability for IMT and SAC, with a coefficient of variation of 2.8% and 9.2%, respectively (28).

Statistical Analysis

All parameters were normally distributed. The Student unpaired *t* test was used to compare differences in mean values for group characteristics, lipids, IMT and SAC measurements overall and for smoking and nonsmoking groups. An analysis of variance (ANOVA) was applied to further assess the interaction between HRT and smoking on IMT and SAC. Independent associations of estrogen use were assessed by multiple linear regression with all measures entered as continuous variables. Regression models based on cardiovascular risk factors incorporating age, body mass index, blood pressure variables and lipid profiles were used to examine the independent relationships between IMT, SAC, lipids and HRT status. With SAC analyses blood pressure parameters were excluded in the statistical model, as calculation of SAC is based on blood pressure. All analyses were performed by using the SPSS statistical package version 8. Data are given as mean ± SEM.

RESULTS

Baseline characteristics. Characteristics including age, height, weight, body mass index and blood pressure parameters were similar in the HRT and control groups overall as well as in smokers and nonsmokers (Table 1). Duration of HRT was similar in the smokers compared with nonsmokers (79 ± 11 vs. 80 ± 2 months, p = 0.9).

Lipid profiles. Mean plasma total and LDL cholesterol was significantly lower and HDL cholesterol was higher in those on HRT compared with control subjects (Table 2). In smokers, those on HRT had lower total cholesterol, but there were no significant differences between smokers on HRT and non-HRT control subjects for mean values of LDL, HDL and triglycerides. In nonsmokers total and

Table 2. Lipid Profiles: HRT Versus Control Subjects in All Subjects and in Smokers and in Nonsmokers

	All Subjects			Smokers			Nonsmokers		
Characteristics	**HRT**	**Controls**	**p Value**	**HRT**	**Controls**	**p Value**	**HRT**	**Controls**	**p Value**
Total cholesterol (mmol/liter)	5.8 ± 0.1	6.6 ± 0.1	0.001	6.0 ± 0.2	6.8 ± 0.3	0.03	5.7 ± 0.2	6.5 ± 0.3	0.02
LDL cholesterol (mmol/liter)	3.5 ± 0.1	4.2 ± 0.2	0.007	3.6 ± 0.2	4.0 ± 0.2	0.2	3.4 ± 0.2	4.4 ± 0.3	0.01
HDL cholesterol (mmol/liter)	1.8 ± 0.1	1.6 ± 0.1	0.02	1.7 ± 0.1	1.6 ± 0.1	0.4	1.8 ± 0.1	1.5 ± 0.1	0.08
Triglyceride (mmol/liter)	1.4 ± 0.1	1.6 ± 0.2	0.4	1.7 ± 0.2	1.8 ± 0.3	0.7	1.2 ± 0.1	1.4 ± 0.2	0.3

Results are presented as mean ± SEM.
HDL = high density lipoprotein; HRT = hormone replacement therapy; LDL = low density lipoprotein.

LDL cholesterol were lower in those on HRT compared with control subjects.

Intima–media thickness. Group and subgroup comparisons for IMT are shown in Table 3 and Figure 1. Mean IMT was similar in smokers and nonsmokers. For all subjects, those on HRT had an IMT lower than that of control subjects. This was seen particularly in the smokers on HRT, where mean IMT was 13% lower than in control subjects not on HRT. The difference in the mean values for nonsmokers was not significant. A subgroup analysis of estrogen versus combined therapy did not reveal any significant differences between these two groups (0.67 ± 0.1 vs. 0.65 ± 0.1 mm, p = NS).

An ANOVA adjusted for cardiac risk factors demonstrated significant interaction between HRT and IMT (p = 0.006); however, smoking status was not significantly correlated with IMT, with the combined interaction term failing to reach significance.

In a stepwise multiple regression analysis, for all subjects, IMT was significantly related to pulse pressure (p = 0.001), HRT status (p = 0.02) and triglyceride level (p = 0.04). In smokers, IMT correlated with systolic blood pressure (p = 0.001), HRT status (p = 0.02) and triglyceride level (p = 0.02); in nonsmokers IMT was correlated only with pulse pressure (p = 0.004).

In those subjects with high total cholesterol (>6.2 mmol/liter, the median for the group), IMT was significantly correlated with systolic blood pressure (p = 0.001) and HRT status (p = 0.01), whereas for those with cholesterol levels ≤6.2 mmol/liter, IMT was correlated only with systolic (p = 0.0001) and diastolic blood pressure (p = 0.01).

Systemic arterial compliance. Group and subgroup comparisons for SAC are shown in Table 3 and Figure 1. Mean SAC was lower in smokers compared with nonsmokers (p = 0.01). For all subjects and for smokers, those on HRT had a more favorable (higher) SAC than control subjects not on HRT. For nonsmokers mean SAC values were similar in the HRT and control subgroups. A subgroup analysis of estrogen versus combined therapy did not reveal any significant differences between these two groups (0.45 ± 0.2 vs. 0.40 ± 0.2, p = NS).

An ANOVA adjusted for cardiac risk factors demonstrated significant interaction between HRT and SAC (p = 0.04) and between smoking status and SAC (p = 0.05), and a significant smoking–HRT interaction term (p = 0.006).

Stepwise multiple regression analysis showed that for all subjects SAC was correlated with age (p = 0.008), HRT status (p = 0.02) and smoking (p = 0.05). In smokers, HRT status was the only significant correlate of SAC (p = 0.0001). In nonsmokers HRT status was not significantly correlated with SAC. In those participants with cholesterol >6.2 mmol/liter HRT use was significantly related to SAC

Table 3. Comparison of Group Values for IMT and SAC

Groups	Subgroups	SAC (U/mm Hg)	p Value	IMT (mm)	p Value
All subjects	Smokers	0.36 ± 0.02		0.70 ± 0.02	
	Nonsmokers	0.44 ± 0.02	0.01	0.69 ± 0.02	0.6
All subjects	HRT	0.43 ± 0.02		0.66 ± 0.01	
	Controls	0.37 ± 0.02	0.06	0.73 ± 0.02	0.006
Smokers	HRT	0.41 ± 0.03		0.64 ± 0.02	
	Controls	0.32 ± 0.03	0.03	0.74 ± 0.03	0.007
Nonsmokers	HRT	0.45 ± 0.03		0.68 ± 0.02	
	Controls	0.43 ± 0.03	0.6	0.72 ± 0.03	0.3

HRT = hormone replacement therapy; IMT = intima–media thickness; SAC = systemic arterial compliance.

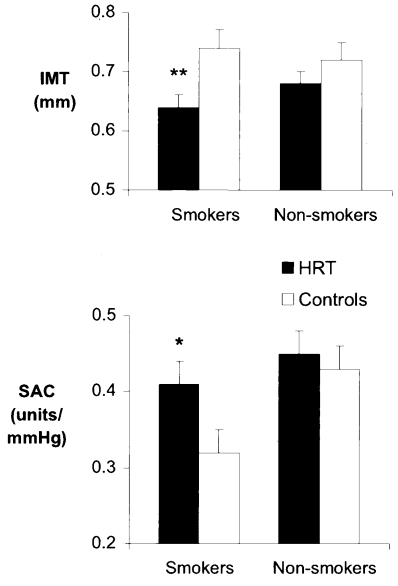

Figure 1. Mean (±SEM) values for intima–media thickness (IMT, **upper panel**) and systemic arterial compliance (SAC, **lower panel**) in smokers and nonsmokers comparing those on long-term hormone replacement therapy (HRT, **solid bars**) vs. control subjects not on HRT (**open bars**). **p = 0.007, *p = 0.03.

(p = 0.004), whereas for those with cholesterol levels ≤6.2 mmol/liter there was no relationship between HRT use and SAC.

DISCUSSION

Smoking and vascular disease. Postmenopausal women who are smokers have double the risk of vascular disease compared with nonsmokers, equivalent to those with diabetes or documented prior myocardial infarction (2,29). Mechanisms contributing to the increased risk in smokers include accelerated atherosclerosis, coronary spasm, thrombosis risk and endothelial dysfunction (13). Smoking also promotes an acceleration of age-related increases in carotid artery IMT (18) that may relate to increased lipid peroxidation (8). Although a major public health goal is to achieve nonsmoking status in the whole community, there is a need for therapies that have cardiovascular protective effects in smokers, including postmenopausal women who smoke.

Although estrogen therapy appears to be cardioprotective in postmenopausal women, there is controversy over whether women who smoke derive equivalent benefits from HRT compared with nonsmokers. Published observational and case–control data are conflicting. Data from the Framingham study suggest that smokers on estrogen have increased cardiovascular mortality (29), whereas all other studies have found no deleterious effects in smokers (1,3,30,31). Many found cardiovascular protection with HRT occurred irrespective of smoking status (1,30). Although it has been suggested that smokers may have reduced benefits compared with nonsmokers (3), it has been noted that estrogen-treated smoking women have a significant reduction in the incidence of stroke, a finding not observed in nonsmokers (31). Disappointingly the majority of observational studies and the only published controlled interventional trial have not specifically addressed the HRT–smoking interaction, largely due to inadequate sample size (1,2,14).

Data interpretation. The results of the present study suggest that postmenopausal smoking women on HRT have significantly more favorable indexes of early atherosclerosis (IMT) and arterial compliance (SAC) compared with age-matched control subjects not on HRT. The apparent beneficial effects of HRT in smokers persisted after correction for other vascular risk factors including blood pressure and plasma lipids. In contrast, nonsmokers on HRT had mean values for IMT and SAC that were similar to those of nonsmoking control subjects. This suggests that those at highest risk may derive greatest benefit from HRT. In keeping with this hypothesis, in those participants with high cholesterol levels (>6.2 mmol/liter), the median value for the whole group, HRT use was significantly related to IMT and SAC, whereas this was not the case for those with lower cholesterol levels. A larger sample size may be necessary to demonstrate apparent vascular benefits of HRT use in postmenopausal women at lower levels of cardiovascular risk (18,32). Likewise, the inability to demonstrate a relationship between smoking and IMT in the present study is likely to be a consequence of the relatively small sample size, given that this has been well defined in large-population studies (33).

In interpreting these results consideration must be given to the potential for bias inherent in all observational studies, specifically, the influence of a "healthy user bias," whereby women choosing to take HRT may vary from those not on HRT, including better general health and level of education (34). The recently published results of the HERS study are also relevant to interpretation of these findings. This controlled, well designed study focused on the secondary prevention of vascular events with combined continuous HRT use in women with established vascular disease (14). No benefits of HRT were seen for a variety of clinical end points including myocardial infarction and cardiac death. There are some caveats to interpreting the HERS study. First, it was a secondary prevention study in women with coronary heart disease and the results cannot be extended to the use of HRT in primary prevention. Second, combined continuous medroxyprogesterone acetate and conjugated equine estrogen was used, a combination recently demonstrated in the cynamologous monkey model to be ineffective in preventing atherosclerosis (35). Thus, there is the potential for differential effects of progestin subtypes and regimens on the vascular system. In the present study we were unable to demonstrate any differences between the estrogen and estrogen plus progestin treatment groups. Medroxyprogesterone acetate was the predominant progestin used in the

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combined HRT group. These results were consistent with our previous findings in a larger cross-sectional study (18). Still, the possibility exists that concomitant use of progestin may tend to counteract the beneficial vascular effects of estrogen in postmenopausal women. Prospective controlled trials are required to address this question. Finally, in the HERS study the mechanisms of HRT action may have been obscured by the extensive therapies already in use in these women, potentially negating any beneficial mechanisms of estrogen action (14).

Mechanisms of estrogen action in smokers. In light of the positive findings presented here, it is interesting to consider the potential mechanisms of estrogen action on the blood vessel wall. Three studies have suggested that HRT affects carotid artery IMT. Manolio et al. (30) reported that estrogen use was associated with reduced IMT after adjustment for other risk factors. In a recent study, our group reported that the age-related increase in IMT and fall in SAC were attenuated in postmenopausal women on HRT (18). Also, in a therapeutic trial of lipid-lowering therapy, Espeland et al. (36) found that women on HRT had a reduced rate of progression of carotid artery IMT. Hormone replacement therapy is likely to exert some of its effects via improved plasma lipids. However, the rapidity with which functional changes can occur (4,5) and the observation from this study that beneficial effects of HRT on IMT and SAC persist after correction for lipid status clearly point toward other mechanisms of action on arteries. Indirect effects via modulation of vascular smooth muscle cells and of the atherosclerotic process (9,10) as well as direct effects on arterial tone and reactivity (37) have been demonstrated. Higher SAC values have been noted in postmenopausal women on HRT, with cessation of therapy leading to a rapid fall in SAC values over four weeks (4). Estrogen therapy can cause acute changes in flow-mediated vasodilation of the brachial artery (5) and influence coronary vasodilation (9), effects that are thought to be mediated by the nitric oxide pathway. Just how estrogen affects endothelial function and arterial compliance, and whether or not these are necessary precursors of the atherosclerotic process, have yet to be determined.

There are several important considerations regarding HRT use in smokers. The first concerns potential harmful effects. An early analysis of data from the Framingham study raised concerns that estrogen may increase vascular disease in all postmenopausal women, especially smokers (29); this report was based on small numbers and subjective end points (chest pain), and has not been confirmed in any other studies. The relative risk of venous thromboembolism in HRT compared with placebo is around 3:1 (14). However, these events are infrequent, with the baseline incidence in postmenopausal women noted at 1 in 10,000 women per year. Unlike high dose oral contraceptive pills, no excess risk has been observed in smokers on HRT (38). Studies on coagulation factors and fibrinolysis have either failed to show an impact with HRT (12), or have demonstrated increased fibrinolytic activity, a possible beneficial mechanism of estrogen action (11). Also, estrogen metabolism is altered in smokers, with dosage requirements, routes of administration and the degree of benefit gained from HRT still uncertain (39,40). In smokers, menopause occurs one to two years earlier (41). Endogenous estrogen levels are lower in smokers (41) with an associated reduction in the incidence of estrogen-associated malignancies (41). In smokers, oral estrogen therapy resulted in lower serum estradiol levels and reduced (but still significant) improvement in both lipid profiles and bone mineral content when compared with those in nonsmokers (39,42). Consistent with this was the observation in the present study that the apparent beneficial effects of estrogen therapy were more evident in smokers than nonsmokers. Interestingly, smokers appear to gain equivalent benefit to nonsmokers if therapy is administered transdermally (39,42).

Conclusions. Existing observational studies in women and animal data strongly support a cardiovascular protective role of HRT. The use of HRT in postmenopausal women who smoke has been limited by lack of evidence and concerns over risks of therapy. In this study, among chronic smokers the use of HRT was associated with a lower mean carotid wall thickness (IMT) and a higher central arterial compliance (SAC), compared with those in smokers not on HRT. These effects persisted after adjustment for other major risk factors and suggest a particular benefit of HRT in smokers. These results need to be interpreted with caution, given the cross-sectional nature of the study and the relatively small sample size.

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Reprint requests and correspondence: Dr. Helena Teede, Vascular Medicine Unit, Department of Medicine, Monash Medical Centre, Clayton, Victoria, 3168 Australia. E-mail: helena.teede@med.monash.edu.au.

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