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Regular exercise, hormone replacement therapy and the age-related decline in carotid arterial compliance in healthy women

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Abstract

Objective: Carotid arterial compliance is reduced with age in sedentary estrogen-deficient women, contributing to the development of cardiovascular disorders. We determined the effects of regular aerobic exercise, hormone replacement therapy (HRT), and their interaction on carotid arterial compliance using a combination of cross-sectional and intervention study designs. **Methods:** Cross-sectionally, we studied three groups of healthy postmenopausal women (50–80 years): 20 sedentary not taking HRT; 24 sedentary taking HRT; and 14 endurance-trained not taking HRT; and 11 sedentary premenopausal controls (20–37 years). In the intervention study, 12 sedentary postmenopausal women (58±3 years) who were taking HRT were studied before and after participation in a 3-month aerobic exercise (walking) program. Carotid arterial compliance was measured via simultaneous common carotid artery ultrasound imaging and applanation tonometry. **Results**: *Cross-sectional study*. Carotid arterial compliance was lower ($P<0.001$) in all three postmenopausal groups compared with premenopausal women. Among the postmenopausal groups, arterial compliance was 33–43% higher in the sedentary HRT and endurance-trained women than in their sedentary estrogen-deficient peers. *Intervention study*. Arterial compliance increased ($P<0.05$) by ~40% to levels that were no longer different than premenopausal women. **Conclusions:** HRT use and regular aerobic exercise are associated with augmented carotid arterial compliance in healthy postmenopausal women. Moderate, short-term aerobic exercise can restore carotid arterial compliance in previously sedentary postmenopausal women taking HRT.

Keywords: Aging; Arteries; Gender; Hormones; Ultrasound

1. Introduction

In sedentary healthy humans, the compliance of the large elastic arteries in the cardiothoracic (carotid) circulation decreases with advancing age [1–3]. The age-related reduction in carotid arterial compliance is associated with functionally and clinically important physiological and pathophysiological consequences within the cardiovascular and autonomic nervous systems including increases in systolic blood pressure [4] and aortic impedance [1,5], left ventricular hypertrophy [1,6], and a decrease in cardiovagal baroreflex sensitivity (CV-BRS) [7]. Via these effects, reduced carotid arterial compliance is thought to play a critical role in the development of several cardiovascular and autonomic disorders including isolated systolic hypertension, orthostatic hypotension, and congestive heart failure.

We recently reported that men who perform regular,

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vigorous exercise demonstrate an attenuated age-related decline in carotid arterial compliance compared with sedentary men [2]. In the same study, we also showed that 12 weeks of moderate aerobic exercise (walking) increased carotid arterial compliance in previously sedentary middle-aged and older men [2]. In contrast to men, little is known about the potentially favorable modulatory effects of habitual exercise on age-associated declines in carotid arterial compliance in healthy women. Similar influences of exercise in females cannot be assumed because of the possible interactive effects of menopause and hormone replacement therapy (HRT) use, which are unique to women.

Accordingly, in the present study we sought to gain insight into the separate and interactive effects of age, HRT, and habitual exercise on carotid arterial compliance in healthy women. To determine the potential beneficial modulatory effects of habitual exercise on age-associated declines in carotid arterial compliance in women, we used both cross-sectional and intervention experimental approaches as described recently for men [2]. In our exercise intervention we specifically sought to determine if regular moderate aerobic exercise could increase carotid arterial compliance even in women who have received some benefit already from being on HRT.

1.1. Methods

1.1.1. Subjects

1.1.1.1. Cross-sectional study Sixty-nine healthy women were studied: 44 sedentary postmenopausal (50–75 years of age) who were either estrogen-deficient ($N=20$, 63 ± 2 years) or taking HRT ($N=24$, 61 ± 2 years) and 14 postmenopausal endurance-trained estrogen-deficient (64 ± 3 years); and 11 sedentary premenopausal controls (28 ± 1 years; range 20–37 years). The endurance-trained subjects were recruited from various running clubs, had been performing regular aerobic exercise (primarily running) an average of 5 ± 1 days/week for at least 5 years, and were active in local road running races. The sedentary subjects were recruited through various forms of advertisements, and did not perform regular exercise of any type. HRT users had been following their regimen for an average of 10 ± 2 years. Sixteen were taking an oral preparation of conjugated estrogens, seven oral estradiol, and one transdermal estradiol. Thirteen of the HRT users were taking a combination of estrogen and progestins (e.g. medroxyprogesterone acetate). Non-users of HRT had not taken any estrogen preparations for at least the past 2 years.

1.1.2. Intervention study

Twelve healthy sedentary postmenopausal women (58 ± 3 years) who were taking HRT an average of 8 ± 2 years were studied before and after a 12-week exercise intervention.

In both studies all subjects were normotensive, nonsmokers, non-medicated (other than HRT), and were free of overt chronic diseases as assessed by medical history, physical examination, standard blood chemistries, and hematological evaluation. Women over the age of 50 years were further evaluated by ECG and blood pressure responses during incremental treadmill exercise to exhaustion. Subjects who demonstrated significant intima-media thickening (>1.5 mm), plaque formation, ankle-brachial pressure index <0.90, and/or characteristics of atherosclerosis were excluded. All subjects gave their written informed consent to participate. The investigation conforms with the principles outlined in the Declaration of Helsinki. All procedures were reviewed and approved by the University of Colorado's Human Research Committee.

1.2. Measurements

All measurements were performed following a 4-h fast (12 h for determination of metabolic parameters) and abstinence from caffeine. Premenopausal women were tested 1–6 days after onset of menstruation (i.e. early follicular phase). Subjects were studied between the hours of 08:00 and 15:00 h; arterial distensibility does not vary over the period [8]. Women in the intervention study were studied at the same time of day before and after the intervention. Endurance-trained women and women participating in the exercise intervention program were studied 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.

1.2.1. Carotid arterial compliance

The combination of ultrasound imaging (Toshiba SSH-140) of the common carotid artery with simultaneous applanation tonometric-obtained arterial pressure waveforms (Millar Instruments SPT-301) from the contralateral artery permits noninvasive determination of carotid artery compliance as previously described [2]. A longitudinal image of the cephalic portion of the carotid artery was acquired ~1 to 2 cm distal to the carotid bulb. The computer images were digitized with a video-frame grabber (Data Translation) and were analyzed using image analysis software as previously described [2]. Time points that corresponded with systolic expansion of the carotid artery and basal diastolic relaxation were selected. Because the baseline levels of carotid blood pressure are subject to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial and diastolic blood pressures to the brachial artery value as previously described [9].

To characterize carotid arterial compliance as comprehensively as possible, three different measures were calculated. Arterial compliance is the change in cross-sectional area of a vessel per unit of pressure, while the

distensibility coefficient is defined as the relative change in cross-sectional area of the vessel per unit of pressure [10]. The beta-stiffness index provides an index of arterial compliance adjusted for distending pressure [11]. The reliability for the measurement of carotid artery compliance in our laboratory is excellent. On nine subjects studied on 2 different days at least 1 week apart the coefficients of variation for the two trials were 2±1, 6±3, and 4±2% for carotid artery diameter, carotid artery pulse pressure, and carotid arterial compliance, respectively.

1.2.2. Brachial blood pressure

Peripheral blood pressure was measured with a semi-automated device (Dinamap, Johnson & Johnson) over the brachial artery as previously described [2].

1.2.3. Metabolic risk factors

Fasting plasma concentrations of cholesterol, glucose, and insulin were measured in the Core-Laboratory within the University of Colorado General Clinical Research Center as previously described [2].

1.2.4. Body composition

Total fat mass and fat-free mass were determined using dual energy X-ray absorptiometry (DPX-IQ, Lunar Corp.).

1.2.5. Maximal exercise capacity

A modified Balke incremental treadmill exercise protocol was used to determine maximal oxygen consumption and time to exhaustion.

1.2.6. Dietary analysis and physical activity levels

Dietary composition and caloric intake were determined from 3-day food intake records (Nutritionist IV software package, based on USDA Handbook #8) [12]. Daily physical activity energy expenditure was estimated using the Stanford Physical Activity Questionnaire [13] as previously described [14].

1.2.7. Exercise intervention

The 3-month exercise intervention was conducted using the same approach as that described in our laboratory in recent investigations [2]. Briefly, the women were asked to walk at a moderate intensity (65–80% of predetermined maximal heart rate) for 40–45 min/day, 4–5 days/week. Adherence to the exercise program was documented through the use of Polar heart rate monitors and physical activity logs as described previously [2].

1.3. Statistical analysis

For the cross-sectional study, a one-way ANOVA was used to assess the effects of age, HRT and endurance-training status. In the case of a significant *F*-value, a Newman-Keuls post-hoc test identified differences among group means. For the intervention study, repeated-measures ANOVA was used to examine the effects of the exercise intervention. Univariate correlation analyses were used to determine the relations between variables of interest.

2. Results

2.1. Cross-sectional study

There were no significant group differences in height, HDL-cholesterol, plasma glucose, diastolic blood pressure, or years of education (Table 1). Body fat was lower and maximal oxygen consumption was higher in premenopausal women and endurance-trained postmenopausal women compared with sedentary postmenopausal women (both $P<0.001$); there were no significant differences between the premenopausal and endurance-trained postmenopausal women. In endurance-trained postmenopausal women, resting heart rate was lower compared with sedentary women ($P<0.001$). Body mass and fasting insulin concentration were lower in endurance-trained compared with sedentary postmenopausal women (both $P<0.01$). Carotid intima-media thickness was greater in postmenopausal compared with premenopausal women ($P<0.001$) regardless of HRT and habitual exercise status. Dietary caloric intake was higher in premenopausal women in comparison to postmenopausal women (2420±90 vs. 1870±53 kcal/day, respectively, $P<0.05$), and was higher in endurance-trained in comparison to postmenopausal HRT (2030±91 vs. 1756±92 kcal/day, respectively, $P<0.05$). There were no differences in macronutrients, sodium, or alcohol intake among the groups (data not shown). Daily physical activity levels were not different among the sedentary groups.

Carotid arterial compliance was lower ($P<0.001$) in the postmenopausal compared with the premenopausal women (Fig. 1a). Among the postmenopausal women, however, carotid arterial compliance was 33–43% higher in sedentary HRT users and endurance-trained groups than in their sedentary, estrogen-deficient peers ($P<0.05$). There was no difference in carotid arterial compliance between sedentary HRT users and endurance-trained postmenopausal women ($P>0.05$). Qualitatively similar results were obtained when the data were expressed as the distensibility coefficient (Fig. 1b) or the beta-stiffness index (Fig. 1c). Carotid pulse pressure was higher in the postmenopausal sedentary non-users (53±3 mmHg) and the endurance-trained women (49±4) than in the premenopausal women (37±2) and postmenopausal HRT users (42±3).

In the pooled population, measures of carotid arterial compliance were related to maximal oxygen consumption ($r=0.33–0.38$, $P<0.05$). No other variables were significantly related to measures of carotid arterial compliance.

Table 1
Selected subject characteristics for the cross-sectional study

Variable	Premenopausal sedentary	Postmenopausal sedentary	Postmenopausal sedentary	Postmenopausal trained
		No-HRT	HRT	No-HRT
n	11	20	24	14
Age, years	28±1	63±2*	61±2*	64±3*
Height, cm	165±3	163±2	162±1	163±1
Body mass, kg	63±3	69±3	68±3	56±1‡
Body fat, %	31±2	38±2*	40±1*	26±2‡
Systolic BP, mmHg	107±2	119±3*	115±2*	124±5*
Diastolic BP, mmHg	64±2	70±2	67±1	69±2
Mean arterial BP, mmHg	78±2	87±2*	84±1	87±2*
Heart rate, beats/min	69±2	65±2	66±2	56±2‡
Total-cholesterol, mmol/l	3.8±0.4	5.2±0.3*	5.1±0.2*	4.5±0.2
HDL-cholesterol, mmol/l	1.3±0.1	1.7±0.1	1.6±0.1	1.5±0.1
Fasting insulin, μU/l	6.9±0.7	7.6±0.3	5.0±0.3†	4.2±0.4‡
Fasting glucose, mmol/l	4.7±0.2	4.8±0.4	4.6±0.2	4.8±0.1
Carotid IMT, mm	0.41±0.02	0.62±0.02*	0.60±0.02*	0.59±0.03*
VO_{2max}, ml/kg/min	35±2	23±2*	23±1*	34±2*†
Physical activity, kcal/kg/day	38.7±1.0	35.5±0.7	36.7±1.5	–
Education, years	16±1	16±1	17±1	16±1

*$P<0.05$ vs. Premenopausal; †$P<0.05$ vs. sedentary postmenopausal; ‡$P<0.05$ vs. all other groups. BP, blood pressure; IMT, intima-media thickness; VO_{2max}, maximal oxygen consumption.

2.2. Intervention study

The sedentary HRT postmenopausal women who participated in the home-based exercise intervention walked an average of 4.9±0.5 days/week, 40±2 min/day, at 70±1% of maximal heart rate for 13±1 weeks. As shown in Table 2, levels of maximal oxygen uptake increased by 6% ($P<0.01$), and total time to exhaustion on the maximal exercise test increased by ~20% ($P<0.005$). No other significant changes were observed.

Following the program of regular exercise, both carotid artery compliance and distensibility coefficient increased by 40% and beta-stiffness index decreased by ~25% (Fig. 2; all $P<0.05$). The absolute values for arterial compliance, distensibility coefficient, and beta-stiffness index after the intervention were higher than those of the sedentary HRT and endurance-trained postmenopausal group values from the cross-sectional study ($P<0.05$), and, importantly, were not different from the values for the premenopausal women ($P=0.24$–0.62). There were no significant changes in carotid pulse pressure before and after exercise intervention (37±4 vs. 31±2 mmHg; $P>0.05$). The improvement in carotid arterial compliance was not related to changes in body composition, plasma lipoproteins, fasting plasma insulin and glucose, arterial blood pressure, dietary intake, or aerobic fitness.

3. Discussion

The primary findings of the present study are as follows. First, carotid arterial compliance is greater in postmenopausal women who use HRT and those who perform regular aerobic exercise than in their sedentary estrogen-deficient peers. Second, a short-term moderate aerobic exercise program restores carotid arterial compliance in healthy, previously sedentary, HRT-supplemented postmenopausal women to levels observed in premenopausal women, consistent with an additive effect. These results suggest that both HRT and habitual exercise have beneficial effects on carotid arterial compliance, and that a short-term aerobic exercise program can reverse the age-related reduction in carotid arterial compliance in HRT-supplemented postmenopausal women.

Little information exists on the effects of regular exercise on carotid arterial compliance, particularly in women. To our knowledge the only published study in women is from our laboratory in which carotid arterial stiffness (measured via aortic pulse wave velocity and augmentation index) was lower in endurance-trained compared with sedentary postmenopausal females [14]. We recently demonstrated that endurance-trained older men have a higher carotid arterial compliance compared with age-matched sedentary controls, and that the age-related reduction in carotid arterial compliance is partially reversed in middle-aged and older men following a 13-week intervention consisting of moderate-intensity aerobic exercise [2]. The results of the present study are consistent with and extend these findings in healthy men. First, our cross-sectional group comparisons allowed us to determine if chronic HRT use and habitual exercise are similarly associated with enhanced carotid artery compliance among healthy postmenopausal women; HRT use has previously been associated with reduced arterial stiffness [15,16]. We found that the age-related reduction in carotid arterial compliance is attenuated in both postmenopausal women who use HRT

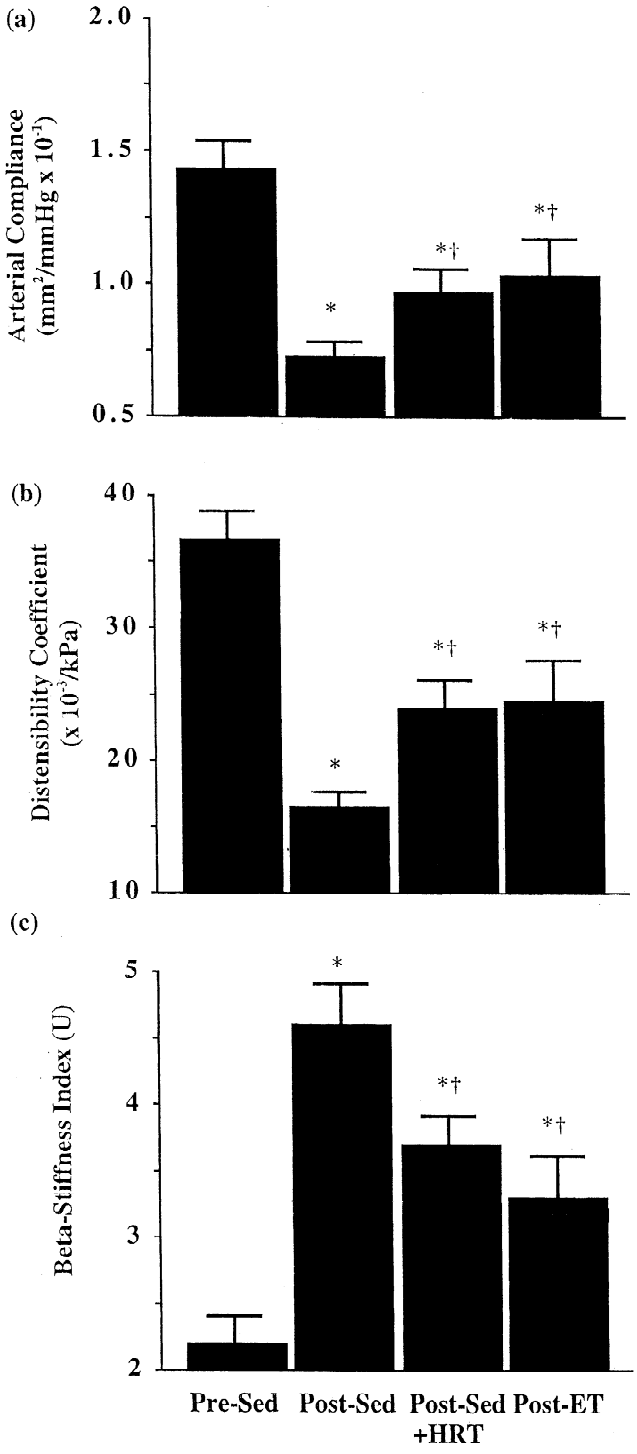

Fig. 1. Arterial compliance (a), arterial distensibility coefficient (b), and beta-stiffness index (c) of women in the cross-sectional study. * $P<0.001$ vs. Pre-Sed; †$P<0.05$ vs. Post-Sed. Pre, premenopausal; Post, postmenopausal; HRT, hormone replacement therapy; ET, endurance training.

and those who participate in regular and vigorous endurance exercise. Second, our intervention study demonstrated that carotid arterial compliance was restored to premenopausal levels after 3 months of exercise in postmenopaual women who were using chronic HRT, whereas

Table 2
Subject characteristics for postmenopausal women who participated in the intervention study

Variable	Before training	After training
Age, years	63±2	–
Height, cm	163±2	–
Body mass, kg	72±5	71±7
Body fat, %	41±2	38±2
Systolic BP, mmHg	115±5	114±5
Diastolic BP, mmHg	67±2	67±1
Mean arterial BP, mmHg	84±3	82±3
Heart rate, beats/min	66±2	63±3
Total-cholesterol, mmol/l	5.3±0.3	5.3±0.5
HDL-cholesterol, mmol/l	1.6±0.1	1.6±0.1
Fasting insulin, μU/l	5.8±0.6	6.3±0.9
Fasting glucose, mmol/l	4.9±0.1	4.8±0.2
Carotid IMT, mm	0.59±0.3	0.58±0.3
VO_{2max}, ml/kg/min	23.5±0.9	25.0±1.0*
Time to exhaustion, min	10.3±0.7	12.3±0.5*

* $P<0.05$ vs. before. BP, blood pressure; IMT, intima-media thickness; VO_{2max}, maximal oxygen consumption.

the same exercise program only partially restored carotid compliance in healthy middle-aged and older men [2]. The enhanced carotid arterial compliance associated with habitual exercise was independent of changes in body composition, diet and traditional CVD risk factors, suggesting a primary effect of regular exercise on the arterial wall. Importantly, the exercise program which consisted of moderate intensity walking is consistent with that recommended by health care organizations for general health maintenance [17,18]. Our findings suggest a possible interactive effect of HRT and exercise on carotid arterial compliance; this may explain the more complete restoration of arterial compliance in postmenopausal HRT users than we observed with this exercise program alone in men [2]. Specifically, although the increase in arterial compliance with the exercise intervention was similar to what we observed in men [2], the fact that baseline levels of carotid compliance were higher (presumably due to chronic HRT use) allowed our women to improve to values seen in premenopausal females. Our results provide initial insight into the potential benefits of using a mutifactorial risk intervention approach [19] to restore the age-related loss in large artery compliance in women. However, in order to accurately determine the separate and interactive effects of HRT and exercise on carotid arterial compliance, randomized placebo controlled intervention trials need to be performed.

The mechanisms by which HRT and regular aerobic exercise increase carotid arterial compliance have not been established. Arterial compliance can be altered over a short time period by changes in the contractile state of the vascular smooth muscle cells [20,21]. In this context, both HRT and habitual exercise increase nitric oxide bioavailability in the vascular endothelium of conduit arteries [22,23], which would, in turn, reduce expression and

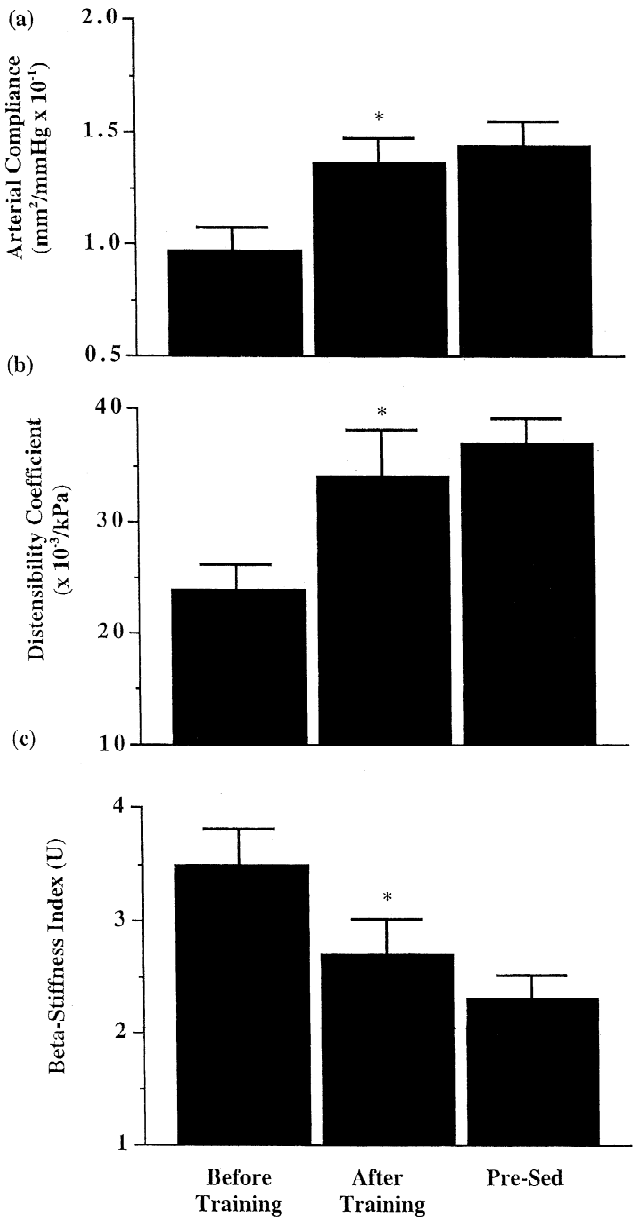

Fig. 2. Arterial compliance (a), arterial distensibility coefficient (b), and beta-stiffness index (c) in sedentary postmenopausal women taking HRT before and after the 3 month aerobic exercise intervention, and in premenopausal women. * $P<0.05$ vs. Before training.

release of the key endothelium-derived constricting factor, ET-1 [24,25]. An increase in the NO:ET-1 ratio would act to increase the tonic state of relaxation of vascular smooth muscle cells in the large elastic arteries, thereby increasing arterial compliance. Additionally, HRT either via direct central nervous system actions or via peripheral vasodilation and alterations in baroreflex stimulation, could lower peripheral sympathetic nerve activity. This would reduce tonic α-adrenergic receptor mediated contraction of vascular smooth muscle cells and increase carotid arterial compliance [26–28]. Structural determinates of large artery compliance also may be involved. Both estrogen and regular exercise have been shown to influence the arterial wall properties by increasing elastin content and inhibiting collagen synthesis [29,30]. Although these mechanisms could explain our cross-sectional group differences in carotid arterial compliance, such structural changes likely require a period of years. Thus, it is unlikely that the improvements with our 3-month exercise intervention involved these mechanisms, but a reduction in the cross-linking of collagen molecules may have contributed. It also is possible that HRT and/or regular exercise may have enhanced the breakdown of advanced glycation end-products in the arterial wall, thereby increasing arterial compliance [31]. Future studies should examine the possible mechanisms associated with HRT and habitual exercise-induced improvements in arterial compliance in large elastic arteries within the cardiothoracic region.

There are at least five important limitations associated with the present study. First, because we used a cross-sectional study design to address the effects of HRT, it is plausible that genetic or other constitutional factors may have influenced carotid arterial compliance. Second, women using HRT are often thought to be 'healthier' and more educated than non-users [32]. To eliminate such constitutional factors as much as possible, we matched the sedentary estrogen deficient and HRT users for age, physical activity and other subject characteristics (e.g. body composition). Third, the inclusion of women using a variety of HRT regimens may have increased inter-subject variability. For example, we were not able to account for the different modes of estrogen therapy regimens. However, when we compared women who used unopposed estrogen with women who used a combination of estrogen and progestin, we found no differences in carotid arterial compliance (data not shown). Fourth, we only studied sedentary hormone replaced women before and after an intervention of moderate aerobic exercise. Thus, our study provides no insight into the ability of short-term exercise training and HRT alone or combined to increase carotid arterial compliance in sedentary estrogen deficient postmenopausal women. Fifth, because we studied only healthy women without evidence of overt chronic diseases or significant intimal-medial thickening, our results can only be generalized to this population. It is possible that HRT and regular aerobic exercise could have different effects on arterial compliance in women with chronic disorders such as cardiovascular diseases and diabetes.

Our findings may have a number of important physiological and clinical implications. The reduction in carotid artery compliance with age is associated with functionally and clinically important physiological and pathophysiological consequences within the cardiovascular and autonomic nervous systems. As such, a reduction in carotid arterial compliance is thought to play an important mechanistic role in the development of age-associated cardiovascular and autonomic nervous system disorders [1]. For example, recent data from our laboratory have demon-

strated that age- and habitual exercise-related differences in carotid arterial compliance are associated with differences in baroreflex sensitivity in healthy men [33], and that that the improvement in baroreflex sensitivity with an aerobic exercise intervention is strongly correlated with the improvement in carotid arterial compliance [33]. Thus, restoring arterial compliance may improve or even normalize cardiovagal baroreflex function. However, we wish to emphasize that because of the recent findings from randomized clinical trials demonstrating no benefit of HRT on coronary heart disease [34–36] and a risk for early harm [34,36], the significance of our HRT results for cardiovascular health should be interpreted cautiously until other ongoing primary prevention trials have been completed. Moreover, combined HRT is associated with other adverse effects including an increased risk for breast cancer [37]. 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. Additionally, because regular exercise is associated with a decreased risk for breast cancer (8, 44), combining both lifestyle behaviors may offset the adverse effects of HRT on breast cancer risk.

In conclusion, the results of the present study support the idea that HRT use and habitual exercise both attenuate the age-related reduction in carotid arterial compliance in healthy women. Furthermore, in postmenopausal women on HRT, a short-term aerobic exercise intervention can restore carotid arterial compliance to levels observed in premenopausal females.

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