Influence of age and postmenopausal estrogen replacement therapy on carotid arterial stiffness in women

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Abstract

Objective: This study examines the influence of age and current estrogen replacement therapy (ERT) on common carotid arterial (CCA) stiffness in women. Methods: The subjects comprised 172 women (age 55.6±16.4 years) from the Baltimore Longitudinal Study of Aging, including 37 current postmenopausal ERT users. The ERT users included 18 women taking estrogen alone and 19 women taking estrogen and progesterone. Bilateral CCA were examined by B-mode carotid ultrasonography, and the stiffness index was defined as the logarithm of the ratio of systolic to diastolic blood pressure (BP) divided by the fractional diameter increase during the cardiac cycle. Results: The stiffness index increased linearly with age (r=0.69, p<0.001), and was lower in ERT users than in postmenopausal nonusers (8.0±2.0 vs 9.7±3.1, p<0.01). Furthermore, the effects of age (β=0.67, p<0.0001) and ERT (β=-0.23, p<0.001) on the stiffness index persisted after adjustments for systolic BP (β=-0.23, p<0.01), diastolic BP (β=-0.26, p<0.001) and other cardiovascular risk factors (model r²=0.59, p<0.0001). The stiffness index was similar in both ERT users with and without progesterone and lower than in postmenopausal nonusers (p<0.05) after considering the age effects. Conclusion: Age-associated increases in CCA stiffness are reduced by postmenopausal ERT. © 1999 Elsevier Science B.V. All rights reserved.

1. Introduction

Cardiovascular disease is the leading cause of death in women, with the risk rising exponentially with age after menopause. Previous studies have shown lower rates of cardiovascular disease in postmenopausal women on estrogen replacement therapy (ERT) than in those not taking it [1,2]. The mechanisms that offer this protection are not completely understood, but include improvements in lipoprotein and carbohydrate metabolism [3], and modulation of the autonomic nervous system [4]. However, estrogen also has direct effects on the arterial wall including vasodilation [5], vascular connective tissue reduction [6] and inhibition of vascular smooth muscle cells [7]. These findings suggest that estrogen should have a favorable influence on the arterial stiffening that occurs with age [8].

Increased arterial stiffness is thought to represent an early risk factor for cardiovascular disease [9,10]. Increased stiffness of large elastic arteries mechanically leads to systolic blood pressure (BP) elevation [11] and left ventricular hypertrophy [12]. Previous studies have shown an association of increased arterial stiffness with atherosclerosis [13], hypertension [14], diabetes [15], hyperlipidemia [16] and smoking [17]. It is also associated with the C allele of angiotensin II type 1 receptor polymorphism [18] which increases the risk of myocardial infarction [19]. Increased arterial stiffness is reported not only in patients...
with coronary artery disease [20] or stroke [21], but also in healthy young subjects with a family history of myocardial infarction [22] or NIDDM [23]. Thus, if postmenopausal ERT reduces arterial stiffness, the reduction may contribute to the cardiovascular protection. Recent studies have suggested an association between ERT and decreased arterial stiffness [24,25]. However, this association is still not established, nor the effect of concomitant use of progesterone.

In the present study, we hypothesized that common carotid arterial (CCA) stiffness increases with age, and current postmenopausal ERT usage is associated with a reduction in the stiffness. To test this hypothesis, we evaluated CCA stiffness in female volunteers from the Baltimore Longitudinal Study of Aging (BLSA) [26]. In addition, we examined the influence of progesterone when used as part of ERT.

2. Subjects and methods

2.1. Subjects

The subjects were female volunteers from the BLSA who were studied from 1995 to 1997. The BLSA consists of community dwelling, predominantly white, college educated volunteers who are studied approximately every two years with 2.5 days of extensive medical, physiological, and psychological examinations.

Each woman was evaluated for menopause status and ERT by interview with an experienced nurse practitioner or a physician assistant. Menopause status was defined by the following criteria: ‘premenopausal’—regular menses in the last 3 months; ‘postmenopausal’—absence of menses in the last 12 months, with or without hysterectomy or bilateral oophorectomy; and ‘perimenopausal’—menses in the last 12 months but with periods of amenorrhea and/or changes in regularity or flow.

Women who had never used ERT were considered ‘nonusers’. Women who were using oral estrogens at the time of evaluation were considered ‘ERT users’. Women who were using only estrogen creams were classified as nonusers, as the effect on circulating estrogen level is small. The ERT users were further divided by the concomitant use of progesterone into ‘E-users’ (estrogen alone) and ‘E+P-users’ (estrogen and progesterone).

Initially, 204 subjects were evaluated for menopause status, ERT and CCA stiffness. However, 24 women who had used ERT but were not currently taking it were excluded, as were three women using estrogen for perimenopausal complaints and three surgically menopausal women younger than 55 years. In addition, two women with >60% internal carotid stenosis were excluded based on duplex ultrasonography.

The study sample consisted of 172 women (age 55.6±16.4 years), including 37 postmenopausal current ERT users (18 E-users and 19 E+P-users) and 135 nonusers (58 pre-, 30 peri- and 47 postmenopausal). None had a stroke history or CCA atherosclerosis (atheromatous plaques or intimal-medial thickening >1 mm). The postmenopausal ERT users and nonusers were comparable in the proportions of subjects on hypertensive, diabetic and hyperlipidemic medications. The duration of ERT usage was longer than six months in all users.

2.2. Carotid arterial stiffness

The CCA was examined bilaterally by high-resolution B-mode ultrasonography with a linear array 5–10-MHz duplex-type scanner (Ultramark 9 HDI, Advanced Technology Laboratories, WA, USA). The examination was performed late in the morning or early in the afternoon with subjects in the supine position in a dark and quiet room. The diameter measurements were started after at least 5 to 10 min of bed rest. The transducer was manipulated so that the near and far walls of the artery were parallel to the transducer footprint and the lumen maximized in the longitudinal plane. No pressure was applied on the skin from the transducer, and acoustic coupling was achieved with gel. A region approximately 1.5 cm proximal to the bulge of bifurcation was identified, and the maximum (systolic) and minimum (diastolic) diameter were measured visually with the help of ECG (in mid- or late-systole, and in end-diastole). It was measured between both endothelial layers, perpendicular to the course of the vessel. The measurements were repeated on three different cardiac cycles for both the right and left CCA. The strain was calculated as the difference between systolic and diastolic diameter (Δd) divided by the average diameter (D). Blood pressure was measured in the brachial artery 15 min after the onset of testing by the oscillometric method (Critikon 1846SX/P, version 085, Dinamap, Tampa, FL, USA).

CCA stiffness was evaluated by the stiffness index which has been validated by Kawasaki [27] and Hirai [20]. It was calculated as follows:

\[ \text{Stiffness index} = \ln \left( \frac{\text{SBP}}{\text{DBP}} \right) / (\Delta d / D) \]

where SBP and DBP are systolic and diastolic BP, and \( \Delta d / D \) is the average strain. All diameter measurements were performed by a trained sonographer (M.K.K) who was unaware of ERT and menopause status of the examinees.

The carotid ultrasound protocols were approved by the Johns Hopkins Bayview Institutional Review Board, and informed consent was obtained from all subjects. The investigation conforms with the principles outlined in the Declaration of Helsinki.

2.3. Statistical analyses

The associations of the stiffness index with age, car-
diovascular risk factors and ERT were evaluated by unpaired t-test and correlation analysis, followed by multiple regression. The risk factors considered in this study were body mass index (BMI), systolic BP, diastolic BP, fasting plasma glucose (FPG), serum total cholesterol (T.Chol), smoking and alcohol drinking. Smokers were defined by past or current smoking ≥10 cigarettes per day, while alcohol usage by ≥1 glass or shot per day of any alcohol beverages. The effect of concomitant progesterone use was assessed by the differences in age-adjusted mean of the stiffness index among E-users, E+P-users and postmenopausal nonusers. Data are presented as mean±SD unless otherwise specified, and a two tailed p value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows 6.1.

3. Results

3.1. Association of the stiffness index with age, cardiovascular risk factors and ERT

Baseline characteristics of the study sample are shown in Table 1. The averages of BMI, systolic BP, diastolic BP, FPG and T.Chol were within the normal ranges in the sample as a whole and in each postmenopausal group. Because the number of current smokers was very low, the presented percentages include both current and past smokers.

ERT users had a lower stiffness index than postmenopausal nonusers (p<0.01). The two postmenopausal groups were comparable in age and the cardiovascular risk factors included in Table 1.

The stiffness index increased linearly with age (r=0.69, p<0.001) in the whole sample, and was modestly correlated with systolic BP (r=0.35, p<0.001), T.Chol (r=0.26, p<0.001) and FPG (r=0.17, p<0.05) but not with BMI (r=0.06, p=0.40) or diastolic BP (r=−0.14, p=0.07). It was similar between smokers and non-smokers (7.5±2.0 vs 7.8±2.7 respectively, p=0.69), and between alcohol drinkers and non-drinkers (8.3±3.2 vs 7.6±2.5, p=0.33).

To further examine the association of CCA stiffness with age and postmenopausal ERT, the stiffness index was simultaneously regressed on age, ERT and the cardiovascular risk factors from Table 1. The stiffness index was strongly and positively associated with age (β=0.67, p<0.0001) and negatively with ERT usage (β=−0.23, p<0.001) when controlling for systolic BP (β=0.23, p<0.01), diastolic BP (β=−0.26, p<0.001), BMI (β=0.05, p=0.37), T.Chol (β=−0.01, p=0.91), FPG (β=0.10, p=0.07), smoking (β=−0.08, p=0.13) and alcohol drinking (β=−0.02, p=0.74) (model r²=0.59, p<0.0001). ERT had no interaction with age and other significant variables.

Fig. 1 shows the age-dependent increase of stiffness index in relation to ERT, demonstrating a lower stiffness index in postmenopausal ERT users than in nonusers.

3.2. Effect of concomitant progesterone use on the stiffness index

As progesterone might attenuate the effect of estrogen on arterial stiffness, ERT users were further divided by the concomitant use of progesterone, and the stiffness index was compared in the postmenopausal women: i.e., E-users (estrogen alone), E+P-users (estrogen and progesterone)
Table 2
Carotid artery stiffness index in postmenopausal women as defined by estrogen replacement therapy with and without progesterone

<table>
<thead>
<tr>
<th></th>
<th>E-users</th>
<th>E+P-users</th>
<th>Nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>19</td>
<td>47</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>7.87</td>
<td>8.27</td>
<td>9.68</td>
</tr>
<tr>
<td>Mean difference*</td>
<td>–</td>
<td>0.40 (−1.05, 1.85)</td>
<td>1.41 (0.21, 2.61)†</td>
</tr>
</tbody>
</table>

E-users: estrogen alone users; E+P-users: estrogen and progesterone users.

* Values represent mean differences (95% CI) in the stiffness index compared to the left adjacent group.

† p<0.05.

and nonusers. The risk factors were similar in all three groups (data not shown). After adjustment for age, the stiffness index was lower in both E-users and E+P-users than in nonusers (p<0.05), but similar between the two user groups (Table 2). Group-age interaction was not observed.

4. Discussion

We have chosen the stiffness index as a measure of CCA stiffness. This index is conceptually similar to the Peterson’s pressure–strain elastic modulus, but has an additional benefit that it is independent of transient changes in BP [20,27]. However, like other indices of segmental arterial stiffness, the stiffness index may compound measurement errors in assessing pressure and diameter. For example, the brachial artery pressure used to calculate this index is not identical to CCA pressure [28]. However, brachial BP determined by the oscillometric method, as in this study, is shown to agree more closely with central arterial pressure than that determined by auscultation [29]. Also, the diameter measurements can be affected by excess transducer pressure over the CCA [30]. To overcome this potential error, our sonographer was instructed to apply the transducer softly without indentation to the skin. Furthermore, despite large intersubject variabilities in the CCA stiffness, Riley et al have shown that only a small fraction of error in assessing the diameter could be attributed to the experimental technique or intra-subject variability [31], supporting the reliability of our CCA stiffness evaluation.

The stiffness index of our study subjects was similar to that reported in the literature [20,27]. The stiffness index increased with age, and current postmenopausal ERT users had a lower index than nonusers (Fig. 1). These findings confirm age-dependent CCA stiffening in women [8], and suggest that postmenopausal ERT mitigates the arterial stiffening. Riley et al. have shown that women younger than 50 years of age have less stiff CCA than men of a comparable age [31] though the difference disappears in older subjects [32]. They speculated that the gender difference is related to female hormones, but no evidence was provided. Our results support the role of estrogen on CCA stiffness. Also, our findings are compatible with the recent studies that have shown reduced aortofemoral pulse wave velocity [24] or increased CCA distensibility coefficient [25] in postmenopausal ERT users compared to nonusers.

Significant associations are known between increased arterial stiffness and traditional cardiovascular risk factors [14–17]. Both systolic and diastolic BP showed a modest association with the stiffness index independent of age and ERT, which was not the case for T.Chol and FPG. The lack of stronger relationships may relate to the overall good health of our subjects which resulted in a narrower range of BP and relatively low T.Chol and FPG levels. Similarly, smoking status was not associated with the stiffness index, which may be due to the low prevalence of current smokers in our study subjects.

Progesterone is sometimes used with estrogen to reduce the risk of uterine cancer. The stiffness index was similarly lower in both ERT users with and without progesterone than in the postmenopausal nonusers (Table 2), suggesting a favorable effect of ERT on arterial stiffness even in the presence of progesterone. Rajkumar et al. showed an increased systemic arterial compliance in ERT users regardless of progesterone use [24], while Liang et al. reported that the favorable effect of ERT on arterial distensibility diminished in the presence of progesterone [25]. Although evaluation methods are not the same between this study and the others, our results are compatible with Rajkumar et al.

Certain limitations should be recognized in the present study. Menopause status was evaluated by menstruation history, and data were not available to examine the relationship between serum estrogen concentration and CCA stiffness. Secondly, this study focused on current ERT usage, but longterm ERT usage in the past might also affect arterial stiffness by changing the wall composition [6]. Further studies are necessary to examine these relationships.

In summary, this study demonstrates age-dependent CCA stiffening in women, and found that postmenopausal ERT reduces the arterial stiffness, a purported cardiovascular risk factor [9,10]. This finding suggests that the effect of ERT on cardiovascular protection may involve alteration of age-associated arterial stiffening.

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