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# Menopausal Status and Distensibility of the Common Carotid Artery

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***Abstract***—Although several studies have shown that exogenous estrogens have beneficial effects on arterial characteristics, the effect of endogenous estrogen on the vascular system is still unknown. In this study, distensibility, an indicator of arterial elasticity, of the common carotid artery was compared in pre- and postmenopausal women. The study comprised 93 premenopausal and 93 postmenopausal women of similar age (range, 43 to 55 years). Women were selected from respondents to a mailed questionnaire about the menopause, which was sent to all women aged 40 to 60 years in the Dutch town of Zoetermeer (n=12 675). Postmenopausal women who were at least 3 years past natural menopause or whose menses had stopped naturally before age 48, were age-matched with premenopausal women with regular menses and without menopausal complaints. The selection aimed at maximizing the contrast in estrogen status between pre- and postmenopausal women of the same age. Distensibility of the carotid artery was measured noninvasively with B-mode ultrasound and a vessel wall movement detector system. Arterial distensibility is expressed as the change in arterial diameter (distension, ΔD) with the cardiac cycle, adjusted for lumen diameter, pulse pressure, and mean arterial blood pressure. Compared with premenopausal women, postmenopausal women had significantly lower arterial distension (ΔD 370.5 $\mu$m [SE 9.5] versus 397.3 $\mu$m [SE 9.6]). These results suggest that the distensibility of the common carotid artery is negatively affected by natural menopause in presumed healthy women. **(*Arterioscler Thromb Vasc Biol*. 1999;19:713-717.)**

**Key Words:** menopause ■ distensibility ■ stiffness ■ carotid artery ■ cardiovascular disease

The incidence of cardiovascular disease in women rises sharply after middle age, and menopause is thought to be a major determinant of this increase.[1–3] The mechanism through which menopause exerts its effect on the cardiovascular system remains largely unexplained. Unfavorable effects on lipid metabolism have been considered a major intermediary. However, recent studies have increasingly emphasized the direct beneficial effects of estrogens on the arterial wall. In experimental studies in animals, estrogen replacement had direct vasodilatory effects[4–6] and was shown to affect the structure and mechanical properties of large arteries. Improved endothelial function has been shown after hormone replacement therapy in women[7–9] and after estrogen use in transsexual men.[10,11] Use of estrogens in premenopausal women with coronary artery disease had a beneficial effect on exercise induced myocardial ischemia.[12]

Few studies have addressed the effects of endogenous estrogens and natural menopause on the dynamic characteristics of the arterial system. Although changes in distensibility were not found during the menstrual cycle,[13] going through menopause has shown to negatively affect the elastic properties of the aortic root in hypertensive women,[14] and time since menopause was inversely related to the pulsatility index in the carotid arteries[15] and several parameters of aortic flow.[16] In the current study, we examined the relation between natural menopause and arterial distension in the common carotid artery.

## Methods

### Study Population

Selection of participants in this study was aimed at maximizing the contrast in estrogen status in pre- and postmenopausal women of the same age (Figure 1). A questionnaire was sent by mail to all women aged 40 to 60 years living in the Dutch town of Zoetermeer, The Netherlands (n=12 675). The questionnaire included questions about menopausal status, medical history, medication use, and smoking behavior. The response rate was 54%. The selection of pre- and postmenopausal women was based on the questionnaire. Women with a hysterectomy and/or unilateral or bilateral oophorectomy (n=1551) and women with missing information on type or date of menopause (n=233) were excluded. Women who had 1 or more bleedings in the past 12 months were considered premenopausal (n=3829). Premenopausal women who reported irregular monthly bleeding (n=938) and women who reported the presence of climacteric symptoms, defined as perspiration and/or hot flushes (n=1645), were excluded from the current study. Furthermore, premenopausal

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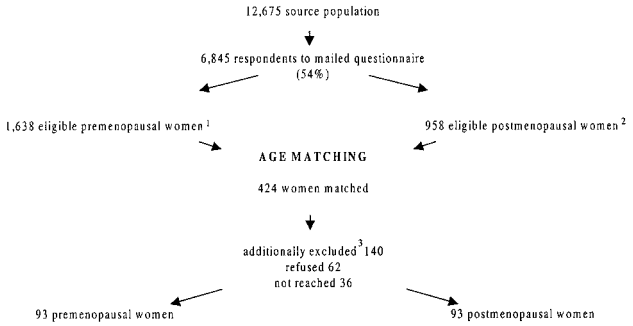


**Figure 1.** Schematic presentation of the selection procedure of the study population. 1, Eligible were women with regular menses and no climacteric symptoms who did not use hormone replacement therapy or oral contraceptives in the past 6 months. Subsequently women who smoked, who had diabetes mellitus, or who used antihypertensive or cholesterol lowering drugs were excluded. 2, Eligible were women whose menses had ceased naturally more than 12 months ago and who had not used hormone replacement therapy. Subsequently women who smoked, who had diabetes mellitus, or who used antihypertensive or cholesterol lowering drugs were excluded. 3, Women who no longer fulfilled the criteria at the moment of examination were excluded.

women who reported use of hormone replacement therapy or use of oral contraceptives within 6 months before the onset of the clinical examination were excluded (n=423). The total number of premenopausal women excluded for the above mentioned reasons was 2191, leaving 1638 eligible premenopausal women.

Women were considered to have had natural menopause if their menses had ceased naturally for at least 12 months (n=1242). Women who reported a history of hormone replacement therapy for over 6 months or use of female hormones within 6 months before the onset of the clinical examination and women who reported cessation of bleeding immediately on stopping hormones were excluded (n=241). The total number of postmenopausal women excluded, including those with missing values on hormone use, was 284, leaving 958 eligible postmenopausal women.

Of the remaining women, we additionally excluded women reporting diabetes mellitus (13 [0.8%] premenopausal and 16 [1.7%] postmenopausal women), use of antihypertensive medication (31 [1.9%] premenopausal and 35 [3.7%] postmenopausal women), use of cholesterol lowering drugs (3 [0.2%] premenopausal and 20 [2.1%] postmenopausal women), and current smoking of ≥5 cigarettes per day (302 [18.4%] premenopausal and 218 [22.8%] postmenopausal women).

To create a sharp contrast in estrogen status we selected women with either an early or a late natural menopause. Postmenopausal women who were ≥3 years after menopause or whose menses had stopped ≥3 years before the average age of menopause (51 years) were age-matched with premenopausal women with regular menses and without menopausal complaints. If it was not possible to find a match within the same year of age, a match was taken from an adjacent year. If 1 of a matched pair was unwilling to participate, a new match was sought. Women were invited for study participation on average 15 months after return of the questionnaire. Out of 424 invited women, 138 were excluded because they no longer fulfilled the inclusion criteria, or no proper replacement match could be found. The primary reasons for no longer fulfilling the inclusion criteria were irregular menses or climacteric symptoms (n=62) and use of female hormones (n=26). Additionally, we excluded women with a history of cardiovascular disease (1 woman with myocardial infarction and 1 with stroke). Sixty-two women (15%) were unwilling to participate and 36 could not be reached. This left 93 pre- and 93 postmenopausal women aged 43 to 55 years who participated in the study. All women gave written informed consent, and the study was approved by the appropriate local institutional committees on ethical practice.

## Measurements

During a visit at the research center, a medical history was taken by a physician. Height, weight, and waist and hip circumference were measured with indoor clothes without shoes. Body mass index (weight/height$^2$) and waist to hip ratio were computed. Data on alcohol drinking habits and cigarette smoking history were obtained by a questionnaire. Serum total cholesterol was measured with an automated enzymatic method using the CHOD-PAP High Performance reagent kit from Boehringer Mannheim.

The vessel wall motion of the right common carotid artery was by means of a Duplex scanner (ATL Ultramark IV, operating frequency 7.5 MHz) connected to a vessel wall movement detector system (Wall Track System). The details of this technique have been described elsewhere.[17,18] Briefly, this system enables the transcutaneous assessment of the displacement of the arterial walls during the cardiac cycle and, hence, the time-dependent changes in arterial diameter relative to its diastolic diameter at the start of the cardiac cycle. Subjects were instructed to refrain from smoking and consuming coffee, tea, alcohol, or pain medication on the day of measurement and from taking alcohol on the day before. Subjects were placed in supine position with the head tilted slightly to the contralateral side for the measurements in the carotid artery. A region at 1.5 cm proximal to the origin of the bulb of the carotid artery was identified using B-mode ultrasonography. Based on the B-mode recording an M-line perpendicular to the artery was selected, and the received radio frequency signals were recorded over 5 cardiac cycles and digitally stored. The displacement of the arterial walls was obtained by processing the radio frequency signals originating from 2 selected sample volumes positioned over the anterior and posterior walls. The successive values of the end-diastolic diameter, the absolute stroke change in diameter during systole ($\Delta D$), and the relative stroke change in diameter ([$\Delta D$]/end-diastolic diameter) were computed from the recording during 5 cardiac cycles. With this system a wall displacement of a few micrometers can be resolved.[17] All measurements were performed by a single observer. A reproducibility study was performed in which 14 participants underwent a second examination within 1 month from the initial examination of the right carotid artery. The coefficient of variation for the absolute diameter change and the lumen diameter was 8.5% and 1.2%, respectively. Measurements were restricted to the right side to save time, as no significant differences in artery wall properties between the right and the left common carotid artery were found.

At the time of the ultrasound examination, blood pressure was measured with a Dinamap automatic blood pressure recorder. Blood pressure was read 4 times at the right upper arm during the measurement session, and the mean was taken as the subjects reading. Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure. Mean arterial pressure was calculated as diastolic blood pressure+(pulse pressure/3).

## Statistical Analysis

Linear regression analysis was used to estimate the differences in characteristics between pre- and postmenopausal women. The difference in distension of the carotid arteries between pre- and postmenopausal women was also estimated using linear regression analysis with distension as the dependent variable. Adjustments were made for diastolic lumen diameter and pulse pressure by including these parameters as independent variables in the regression model. This component model allows the inclusion of mean arterial pressure as an additional covariate to account for its effect as well as for pulse pressure.[19–21] Also, additional adjustment could be made for age.

In a separate analysis, the relation between distension and time since menopause was estimated using linear regression analysis adjusting for age, diastolic lumen diameter, pulse pressure, and mean arterial pressure. As the dependent variable, a newly created ordered variable was used, which consisted of the following 3 groups of postmenopausal women: women up to 4 years after menopause, women 5 to 8 years after menopause, and women 9 to 12 years after menopause. A test of significance for the coefficient of this ordered variable was considered to be a test for trend. If a woman could recall the year but not the exact date of onset of menopause, the date was approximated and set on the first of July of that year. Statistical significance was considered to be present when $P<0.05$.

**TABLE 1. General Characteristics of Pre- and Postmenopausal Women**

| | Premenopausal (n=93) | Postmenopausal (n=93) |
|---|---|---|
| Mean (SD)* | | |
| Age, y | 50.6 (2.4) | 51.1 (2.2) |
| Height, cm | 166.8 (5.7) | 165.6 (7.3) |
| Weight, kg | 68.8 (11.1) | 68.6 (11.5) |
| Body mass index, kg/m$^2$ | 24.7 (3.8) | 25.0 (4.0) |
| Cholesterol, mmol/L | 5.9 (1.0) | 6.5 (0.9)‡ |
| Alcohol, grams/wk | 45 (57.0) | 45 (57.1) |
| Percentage (n) | | |
| Current smoking, %† | 6 (6) | 6 (6) |
| Past smoking, %† | 42 (39) | 39 (36) |

*All variables were adjusted for age, with exception of alcohol and smoking; †Subjects who smoked 5 or more cigarettes per day were excluded from study participation.
‡$P<0.001$.

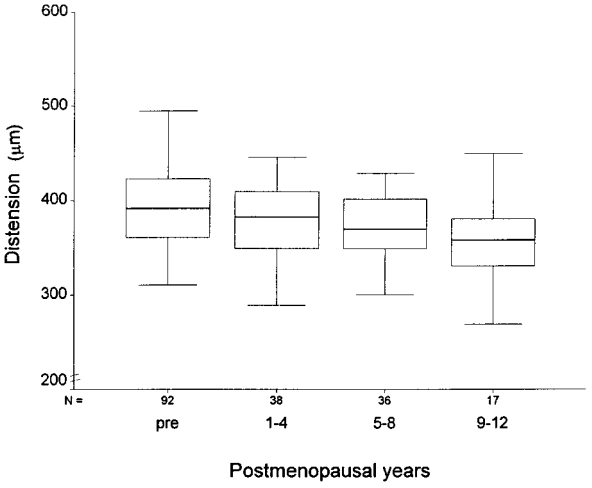


**Figure 2.** Distension, adjusted for diastolic lumen diameter, pulse pressure, and mean arterial pressure, in premenopausal and 3 groups of postmenopausal women (test for trend, $P=0.22$).

## Results

General characteristics of pre- and postmenopausal women are outlined in Table 1. Among postmenopausal women, the mean number of years after menopause was 5.4 (SD=3.0), and ranged from 1.3 to 12.8. Age, height, weight, body mass index, waist hip ratio, alcohol consumption, smoking, blood pressure, and pulse pressure and frequency were not significantly different between the t2 groups (Table 1 and 2). Total cholesterol was significantly higher in postmenopausal women. The end-diastolic lumen diameter was larger in postmenopausal women (6.73 mm) compared with premenopausal women (6.59 mm), but this difference did not reach statistical significance (Table 2).

When comparing the 2 study groups, a significant 7.2% decrease in distension was found in postmenopausal women (ΔD 370.5 μm [SE 9.5]) compared with premenopausal women (ΔD 397.3 μm [SE 9.6]), adjusted for age, diameter during diastole, pulse pressure, and mean arterial pressure (Table 2).

When women were categorized in 3 groups by time since menopause, distension in women up to 4 years after menopause was 379.6 μm (SE 15.9), in women 5 to 8 years after menopause distension was 371.0 μm (SE 15.4), and in women 9 to 12 years after menopause distension was 359.6 μm (SE 22.9), adjusted for age, diastolic lumen diameter, pulse pressure, and mean arterial pressure (Figure 2). This shows that distension tended to decrease with time since menopause, but the changes did not reach statistical significance (test for trend $P=0.22$).

## Discussion

The results of the current study show that the distensibility of the common carotid artery is significantly lower in postmenopausal women than in premenopausal women of the same age, indicating increased arterial stiffness after menopause.

In studying the effect of menopause, age is an important confounding factor. By a rigorous selection procedure in the current study, we composed a population of age-matched pre- and postmenopausal women from a general population. Because of our stringent inclusion and exclusion criteria, the effect of misclassification of menopausal status is likely to be small. Some misclassification of age of menopause may have occurred, as these assessments were based on self-reports. The slight age difference between the study groups after age-matching was dealt with by further adjustment in the analyses. To exclude potential bias due to other factors, such

**TABLE 2. Arterial Characteristics in Pre- and Postmenopausal Women**

| | Premenopausal (n=93) | Postmenopausal (n=93) | | | |
|---|---|---|---|---|---|
| | Mean (SE) | Mean (SE) | Difference | (95% CI) | *P* Value |
| ΔD, μm* | 397.3 (9.6) | 370.5 (9.5) | −26.8 | (−53.5–0.19) | 0.05 |
| ΔD/D, %† | 6.0 (0.14) | 5.6 (0.14) | −0.39 | (−0.78–0.00) | 0.05 |
| Diastolic lumen diameter, mm‡ | 6.6 (0.06) | 6.7 (0.06) | 0.14 | (−0.04–0.32) | 0.12 |
| Systolic blood pressure, mm Hg‡ | 120.8 (1.5) | 120.6 (1.5) | −0.14 | (−4.30–4.01) | 0.95 |
| Diastolic blood pressure, mm Hg‡ | 67.7 (1.0) | 68.6 (1.0) | 0.90 | (−1.97–3.77) | 0.54 |
| Mean arterial pressure, mm Hg‡ | 85.4 (1.1) | 86.0 (1.1) | 0.55 | (−2.50–3.60) | 0.72 |
| Pulse pressure, mm Hg‡ | 53.0 (1.1) | 52.0 (1.1) | −1.04 | (−4.02–1.93) | 0.49 |
| Pulse frequency, beats/min‡ | 67.4 (0.1) | 67.0 (0.1) | −0.43 | (−2.92–2.06) | 0.74 |

*Adjusted for age, pulse pressure, mean arterial pressure, and diameter; †Adjusted for age, pulse pressure, and mean arterial pressure; ‡Adjusted for age. CI indicates confidence interval.

as smoking, lipid lowering medication, antihypertensive medication, current or recent use of hormone replacement therapy or oral contraceptives, or diabetes, we excluded all women with 1 or more of these confounders and furthermore restricted the study to women who had experienced a natural menopause.

We measured distension in the carotid artery and adjusted for pulse pressure measured in the brachial artery. We thereby assume that pulse pressure measured in the brachial artery is representative of pulse pressure in the carotid artery. In dogs, it has been demonstrated that pulse pressure in the brachial artery is linearly related to blood pressure in the carotid artery over a wide range of blood pressures.[22] It is known that the arterial pressure waves undergo transformation in the arterial tree, and therefore, the pulse pressure is higher in the brachial artery than in more central vessels.[23] With increasing age, however, this difference between central and peripheral pulse pressure decreases. It is not known whether the overestimation of pulse pressure measured at the brachial artery differs between pre- and postmenopausal women. If, in line with the decreasing difference seen with age, the overestimation of pulse pressure is less in postmenopausal women, then the true difference in distensibility between the 2 groups would be even larger than estimated in our study.

Various studies suggest sex differences in mechanical properties of the large arteries during the reproductive years, but not thereafter,[24–26] and a steeper decline in distensibility in women than in men in the age range of 45 to 60 years.[27] This suggests, but does not yet definitively prove, the influence of menopause on artery wall properties. Studies aimed directly on the relation between natural menopause and artery wall properties are limited. Gangar et al[15] found that the pulsatility index, representing impedance to blood flow distal to the point of measurement in the internal carotid artery, decreased with time since menopause. Taquet et al[28] could not show a relationship between menopausal status and aortic pulse wave velocity in 429 women, but the population consisted of perimenopausal women and therefore the contrast in estrogen levels between pre- and postmenopausal women may have been small. In 1 study, a decrease of elastic properties of the aorta was found in a small group of hypertensive women going through menopause during 3 years of follow-up, compared with age-matched women who remained premenopausal during the same period.[14] In our study, decreased distensibility after natural menopause is demonstrated among presumed-healthy women.

The mechanisms through which menopause affects mechanical properties of the arteries are largely unknown. Specific binding of estrogens to receptors in endothelial and vascular smooth muscle cells has been demonstrated in different vascular beds in animals and in humans.[29,30] Estrogen might change the structure of the arterial wall. In vitro investigations as well as animal studies showed that estrogens decrease collagen production and decrease the elastin/collagen ratio.[31–33] We found a slightly increased lumen diameter in postmenopausal compared with premenopausal women, which may be indicative of remodeling of the vessel wall.[34]

Whether loss of distensibility is an early marker for asymptomatic atherosclerotic changes or whether it reflects other structural changes of the arterial wall is still a matter of debate.[35–38] Decreased distensibility is unfavorably associated with age[27,39] and with several cardiovascular risk factors, like cholesterol[40] and hypertension.[28,41] Loss of distensibility in elastic arteries has been shown to be associated with an increased risk of cardiovascular disease in cross-sectional studies.[42,43] Longitudinal data on the effect of decreased distensibility on cardiovascular morbidity or mortality are, however, still awaited.

In conclusion, our findings suggest that natural menopause adversely affects the distensibility of the common carotid artery. This may indicate one of the mechanisms through which menopause adversely affects cardiovascular disease risk in women after middle age.

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