Original Article

Effect of Arterial Lumen Enlargement on Carotid Arterial Compliance in Normotensive Postmenopausal Women

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A reduction in central arterial compliance has been identified as an independent risk factor for future cardiovascular disease. The aim of the present study was to determine the influence of age-related carotid arterial enlargement on carotid arterial compliance in postmenopausal females, using a cross-sectional study design. Carotid arterial properties were measured with applanation tonometry and ultrasound system in 113 normotensive females (aged 50–78). Brachial-ankle pulse wave velocity (baPWV) measured by a plethysmographic technique was used as an index of arterial stiffness. In comparisons among the three age groups (50–59, 60–69, and 70–78 years old), baPWV (F=11.9, p<0.001) and carotid systolic (F=4.5, p<0.05) and pulse pressures (F=9.6, p<0.0001), and lumen diameter (F=5.6, p<0.01) increased with advancing age. Carotid arterial compliance gradually decreased with age, but not significantly. A stepwise regression analysis revealed that carotid systolic pressure and lumen diameter and age were independent correlates of carotid arterial compliance. After carotid lumen diameter was taken into account (ANCOVA), the differences in carotid arterial compliance among the three age groups became significant (F=3.8, p<0.05). These results suggest that an increase in arterial lumen diameter might compensate for the age-related increase in arterial stiffness and limit the deterioration of the buffering capacity of the central artery in normotensive postmenopausal females. (*Hypertens Res* 2005; 28: 323–329)

***Key Words*: carotid artery, remodeling, arterial compliance, aging**

Introduction

Large elastic arteries in the cardiothoracic region such as the aorta and common carotid artery act to buffer flow pulsation at its input (*1*). Arterial compliance, which is a function of both arterial volume and volumetric distensibility, reduces fluctuations in arterial pressure and blood flow. Decreases in central arterial compliance, as observed in sedentary aging, have a number of adverse effects on systemic cardiovascular function (*e.g.*, elevations in systolic blood pressure and pulse pressure, increases in aortic impedance and left ventricular wall tension, and a reduction in arterial baroreflex gain) (*2–4*). These symptoms are associated with diseases such as isolated systolic hypertension, congestive heart failure, left ventricular hypertrophy, and orthostatic and postprandial hypotension. With the recent recognition of high pulse pressure as an independent determinant for cardiovascular disease (*5–7*), the decreased central arterial compliance has been identified as an independent risk factor for future cardiovas-

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Table 1. Subject Characteristics

Variables	Group 1	Group 2	Group 3
N	34	54	25
Age (years)	54.2±0.5	63.8±0.3*	73.2±0.5*,†
Height (cm)	154.1±0.9	151.7±0.6	149.0±1.4*,†
Weight (kg)	55.5±1.4	52.7±0.8	50.4±1.4*
Body mass index (kg/m^2)	23.3±0.5	22.9±0.3	22.7±0.5
Brachial systolic BP (mmHg)	116±2	120±1	124±2*
Brachial diastolic BP (mmHg)	73±1	76±1	73±1
Brachial mean BP (mmHg)	90±2	92±1	94±2
Brachial pulse pressure (mmHg)	43±1	44±1	51±2*,†
Heart rate (bpm)	59±1	63±1	64±2
Total cholesterol (mg/dl)#	209±7	224±5	210±8
HDL cholesterol (mg/dl)#	61±2	63±2	57±2
LDL cholesterol (mg/dl)#	123±6	135±4	130±6
Plasma gulcose (mg/dl)#	93±2	97±1	99±3
Plasma insulin (μU/ml)#	5.7±0.9	6.4±0.5	4.3±0.4

Data are mean±SEM. BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *$p<0.05$ *vs.* group 1, †$p<0.05$ *vs.* group 2. #Nine subjects of group 1 and 1 subject of group 3 did not measure.

cular disease. Previous studies of a wide cross-section of the population spanning several generations indicated that carotid arterial compliance decreases with advancing age (*8*, *9*). In addition, carotid arterial compliance in sedentary postmenopausal women without hormone replacement therapy was shown to be significantly lower than that observed in premenopausal women (*10*). The loss of endogenous estrogen production is thought to induce a decrease in central arterial compliance by advancing deterioration of endothelial function, fibroblast and vascular smooth muscle cell proliferation, and collagen accumulation in the aortic wall, all of which are correlated with the higher incidence of coronary heart disease in females after menopause (*11*). Therefore, to explore the age-related alteration of central arterial compliance after menopause is of both physiological and pathological significance. Nonetheless, very little is known about this issue.

An enlargement of the carotid arterial lumen diameter has been observed in middle-aged and elderly people (*12–15*). As arterial compliance is the product of volume and distensibility, the increased arterial lumen diameter might compensate for an age-induced decrease in distensibility, thereby limiting the reduction in arterial compliance (*1*). However, there have been few experiments addressing this issue in postmenopausal females. The present study explores the effects of age-related enlargement of carotid lumen diameter on arterial compliance in postmenopausal females, using a cross-sectional study design.

Methods

Subjects

We studied 113 normotensive postmenopausal females between the ages of 50 and 78. Subjects were categorized into three age groups: group 1, 50–59 years old; group 2, 60–69 years old; and group 3, 70–78 years old. Physiological characteristics of the subjects are presented in Table 1. None of the subjects had a smoking habit, were taking medications, or were undergoing hormone replacement therapy. Subjects were sedentary or recreationally active and did not take part in regular endurance training (>5 days/week). In addition, none had significant intima-media thickening (>1.1 mm) and/or plaque formation. All potential risks and procedures of the study were explained to the subjects, who gave their written informed consent to participation in the study. This study was reviewed and approved by the Institutional Human Research Committee.

Measurements

All the experiments were done after an overnight fast (>8 h). The subjects abstained from alcohol, caffeine, and vigorous physical activity for at least 24 h before the experiments.

Metabolic Risk Factors

Blood sampling was performed to evaluate metabolic risk factors for cardiovascular disease. Fasting plasma concentrations of total cholesterol, low-density lipoprotein with cholesterol, and glucose were evaluated by the enzymatic method. Fasting plasma concentrations of high-density lipoprotein with cholesterol and insulin were evaluated by the synthetic polymer method and the enzyme immunoassay method, respectively. Nine subjects of group 1 and one subject of group 3 did not undergo blood sampling.

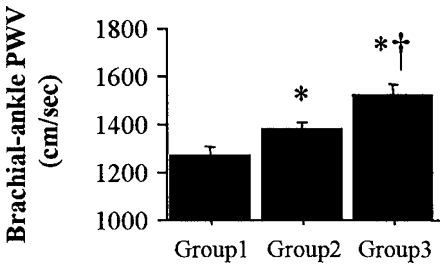

Fig. 1. *Comparisons of brachial-ankle pulse wave velocity (PWV) among age groups.* *p < *0.05* vs. *group 1,* †p < *0.05* vs. *group 2.*

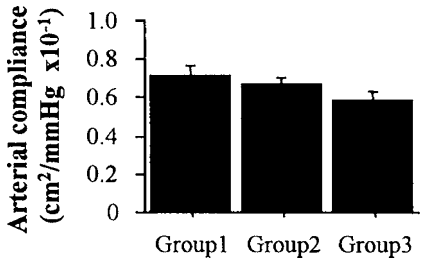

Fig. 2. *Comparisons of carotid arterial compliance among age groups.*

Brachial-Ankle Pulse Wave Velocity (baPWV)

baPWV was measured with a vascular testing device (form PWV/ABI; Colin Medical Technology, Komaki, Japan) in the supine position, as described in detail previously (*16–18*). Extremities cuffs connected to an oscillometric pressure sensor and a plethysmographic sensor were wrapped on both arms and ankles. Brachial blood pressure was measured by the oscillometric method. The bilateral brachial and posterior-tibial arterial pressure waveforms were then stored by the volume plethysmographic method for 10 s. Pulse wave velocity was calculated as the distance between the two arterial recording sites divided by the transit time. Transit time was determined from the time delay between the right brachial and right posterior-tibial arteries (T_{ba}). The foot of the wave was identified as the start of the sharp systolic upstroke, which was automatically detected by a band-pass filter (5–30 Hz). The path lengths from the suprasternal notch to the brachial artery (D_{hb}), from the suprasternal notch to the femur (D_{hf}), and from the femur to the ankle (D_{fa}) were calculated automatically using the following equations:

$$D_{hb} = (0.220 \times \text{height [cm]} - 2.07)$$

$$D_{hf} = (0.564 \times \text{height [cm]} - 18.4)$$

$$D_{fa} = (0.249 \times \text{height [cm]} + 30.7).$$

Finally, baPWV was calculated as

$$\text{baPWV} = (D_{hf} + D_{fa} - D_{hb}) / T_{ba}.$$

Properties of Carotid Arteries

Measurements of carotid artery properties were performed under supine resting conditions after an at least 30-min rest. B-mode longitudinal right common carotid artery lumen diameter and intima-media thickness (IMT) images were measured by an ultrasound system with a high-resolution (10 MHz) linear transducer (SonoSite180PLUS; SonoSite, Inc., Bothell, USA), as previously described in detail (*9*, *10*, *19*). The transducer was placed 1–2 cm proximal to the carotid bulb at a 90° angle to the vessel, and 10–20 pulsations of the common carotid artery were recorded on digital videotape. Ultrasound images were analyzed by image-analysis software (Scion Image; Scion Corporation, Frederick, USA). The IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface at the minimum diastolic relaxation of the artery (*20*). The carotid lumen diameter was determined as the distance between the vessel far-wall boundary (*i.e.*, the interface between the lumen and intima) and the near-wall boundary (*i.e.*, the interface between the adventitia and media) at the minimum diastolic relaxation and at the maximal systolic expansion of the artery, as previously described (*9*, *10*, *19*, *20*). The IMT and carotid lumen diameter at the minimum diastolic relaxation and at the maximal systolic expansion of the vessel were measured at three points per frame and averaged. Three to five continuous data points for each parameter were averaged and statistically analyzed. The IMT/diastolic lumen diameter ratio was also calculated. Carotid arterial compliance was calculated as follows (*9*, *10*, *19*):

$$\text{Arterial compliance} = \{(D_s/2)^2 \times 3.14 - (D_d/2)^2 \times 3.14\} / (P_s - P_d),$$

where P_s and P_d are the carotid systolic and diastolic pressure, respectively, and D_s and D_d are the carotid arterial lumen diameter at the maximal systolic expansion and at the minimum diastolic relaxation, respectively. All scans and image analyses were performed by the same investigator. Pressure waveforms of the left common carotid artery were recorded with an applanation tonometry device (form PWV/ABI; Colin Medical Technology) and calibrated by equating the carotid mean arterial and diastolic blood pressure to that of the brachial artery (*21*). The validity and reliability of this device were proven by a previous study (*22*).

Statistical Analyses

One-way ANOVA was used to compare variables of interest among the three age groups. In the case of a significant F value, a post-hoc test using the Newman-Keuls method identified significant differences among mean values. Univariate correlation analysis was performed to determine relationships between variables of interest. Forward stepwise multiple-regression analysis was used to identify significant independent determinants for arterial compliance. ANCOVA was

Table 2. Carotid Arterial Properties

Variables	Group 1	Group 2	Group 3
Carotid systolic BP (mmHg)	113±3	114±2	123±3*,†
Carotid pulse pressure (mmHg)	39±2	39±1	51±3*,†
Carotid diameter (mm)	5.6±0.1	6.1±0.1*	6.2±0.1*
Carotid IMT (mm)	0.60±0.03	0.63±0.02	0.71±0.03*,†
Carotid IMT/lumen diameter	0.11±0.004	0.11±0.003	0.12±0.006

Data are mean±SEM. BP, blood pressure; IMT, intima-media thickness. *$p<0.05$ *vs.* group 1, †$p<0.05$ *vs.* group 2.

performed to eliminate the influence of one variable from the relationship between two other variables. All data are reported as the mean±SEM. Statistical significance was set at $p<0.05$ for all comparisons.

Results

The subject characteristics are presented in Table 1. Height in the oldest group (group 3) was significantly lower than those in the other groups. Body weight in the oldest group was significantly lower than those in the youngest group (group 1). There were no significant differences in body mass index or metabolic risk factors among the three age groups. Brachial systolic blood pressure in the oldest group was significantly higher than that in the youngest group ($p<0.05$). Brachial pulse pressure in the oldest group was significantly higher than those in the other groups (all $p<0.05$). There were no significant differences in either diastolic or mean blood pressures among the three age groups. baPWV progressively increased with advancing age (all $p<0.05$, Fig. 1).

Carotid arterial compliance was negatively related to age ($r=-0.22$, $p<0.05$). However, there were no significant differences among the three age groups ($F=1.7$, $p=0.18$, Fig. 2). Comparisons of the other carotid arterial properties among the three groups are summarized in Table 2. Carotid systolic and pulse pressures gradually elevated with advancing age ($F=4.5$, $p<0.05$; $F=9.6$, $p<0.0001$; respectively), with subjects in the oldest group exhibiting significantly higher values than those in the other groups (all $p<0.05$). The carotid lumen diameter gradually increased with advancing age ($r=0.28$, $p<0.01$, Fig. 3A), with subjects in groups 2 and 3 exhibiting significantly larger values than those in the youngest group (both $p<0.05$). The carotid lumen diameter was significantly related to carotid systolic blood pressure ($r=0.27$, $p<0.01$, Fig. 3B) and pulse pressure ($r=0.20$, $p<0.05$). The IMT in the oldest group was significantly higher than those in the other groups (all $p<0.05$). There were no significant differences in the IMT/ diastolic lumen diameter ratio among the three age groups.

Table 3 summarizes the univariate relationship of arterial compliance to potential determinants. To identify significant independent determinants for arterial compliance from among these potential determinants, forward stepwise multiple-regression analysis was performed. The results showed that carotid systolic pressure ($\beta=-0.50$, $p<0.0001$), lumen diameter ($\beta=0.40$, $p<0.0001$), and age ($\beta=-0.23$, $p<0.001$) were significant independent determinants of carotid arterial compliance, whereas the other parameters were canceled. After carotid lumen diameter was taken into account (ANCOVA), the age-related difference in arterial compliance among the three age groups became statistically significant ($F=3.8$, $p<0.05$). On the other hand, even after carotid systolic pressure was taken into account, there were no significant differences in arterial compliance among the three age groups ($F=0.5$, $p=0.62$).

Discussion

The principal findings of this study are as follows: no age-related reduction in carotid arterial compliance was observed among groups of postmenopausal females ranging from 50–78 years of age. However, the baPWV, which measures the systemic arterial stiffness, progressively increased with age. A stepwise regression analysis revealed that carotid systolic pressure and lumen diameter and age were significant independent determinants of carotid arterial compliance. After arterial lumen enlargement, but not carotid systolic pressure, was taken into account, the age-related difference in arterial compliance among the three age groups became statistically significant. These results suggest that the enlargement of arterial lumen diameter might compensate for the age-related increase in arterial stiffness, and partly limit the deterioration of the buffering capacity of the central artery in normotensive postmenopausal females.

Many studies have reported that the stiffness of large arterial walls increases (*8–10*, *23–26*) and the compliance of large arteries decreases (*8–10*) with advancing age. In the present study, there were significant differences in baPWV among the three age-decade groups, whereas carotid arterial compliance did not show significant differences even though it significantly correlated with age. These results suggest that the magnitude of reduction in carotid arterial compliance might be smaller than that in arterial stiffness after menopause. Since arterial compliance is the product of volume and distensibility, with distensibility being the absolute change in volume per unit of carotid artery pulse pressure, it is theoretically possible that outward hypertrophic remodeling of the carotid artery could partly inhibit age-related decreases in

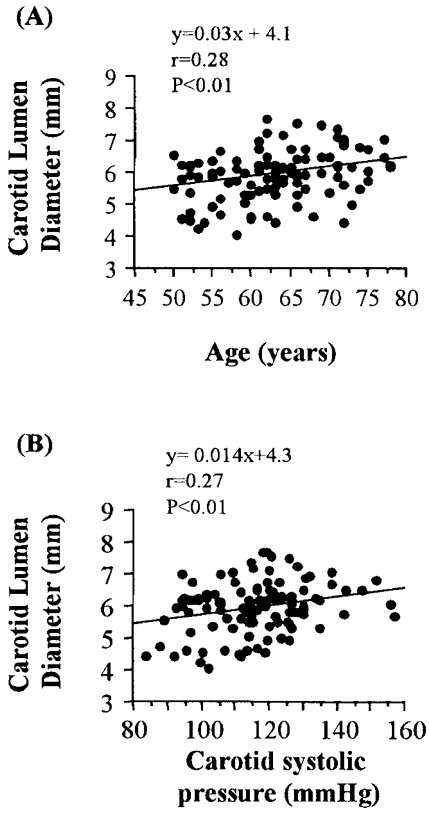

Fig. 3. *Relationship of carotid lumen diameter to age (A) and carotid systolic blood pressure (B).*

Table 3. Univariate Relationship of Arterial Compliance to Potential Determinants

Independent variables	*r*-value	*p*-value
Age	−0.217	<0.05
Brachial systolic BP	−0.244	<0.01
Brachial diastolic BP	−0.102	0.28
Brachial mean BP	−0.265	<0.01
Brachial pulse pressure	−0.268	<0.01
Brachial-ankle PWV	−0.243	<0.01
Carotid systolic BP	−0.356	<0.0001
Carotid pulse pressure	−0.355	<0.0001
Carotid diameter	0.228	<0.05
Carotid IMT	0.064	0.48

BP, blood pressure; PWV, pulse wave velocity; IMT, intima-media thickness.

arterial compliance (*1*). Indeed, in the present study, multiple regression analysis revealed that the carotid arterial lumen diameter was a significant independent correlate of arterial compliance, as was age. These results suggest that, in normotensive postmenopausal females, the buffering capacity of the central artery was reduced with aging, but this effect was partly offset by the enlargement of the carotid artery.

The reasons why the central artery lumen diameter dilates with aging are unclear. However, we observed a weak but significant relationship between the carotid lumen diameter and carotid systolic and pulse pressures. Boutouyrie *et al*. (*27*) indicated that carotid pulse pressure was a strong determinant of carotid artery remodeling. It is known that prolonged local pulsatile and cyclic mechanical load induces structural alterations in the arterial wall, such as hyperplasia of the intima and loss of orderly arrangement of elastin fibers and laminae in the media, including thinning, splitting, fraying, and fragmentation (*28*, *29*). Additionally, degeneration of elastin fibers is associated with an increase in collagenous material and in ground substance, often with deposition of calcium in degenerating fibers (*1*). It is therefore plausible that central arteries dilate as a consequence of these age-related structural alterations (*12–15*). In the present study, both the carotid IMT and the carotid lumen diameter increased with aging. And thereby, the relative wall thickness, which is an independent predictor of left ventricular dysfunction in essential hypertension (*30*), was maintained. Taken together, these findings suggest the possibility that the increased central arterial lumen diameter is a physiological alteration associated with aging, not a pathophysiological state or maladaptation. Decrease in central arterial compliance is associated with several pathological states common to older adults (*i.e.*, isolated systolic hypertension, left ventricular hypertrophy, and congestive heart failure) and has been identified as an independent risk factor for future cardiovascular disease (*31–33*). Accordingly, a small reduction in carotid arterial compliance in middle-aged and elderly people *via* outward hypertrophic remodeling of the carotid artery is favorable for cardiovascular function.

It is well-known that B-mode ultrasound images of the near (more superficial) and far (deeper) walls are different mostly due to the different order in which the interfaces of the intima/lumen and media/adventitia are exposed to the incoming ultrasound beam (*20*). The far wall, but not the near wall, could be consistently and repeatedly visualized. Therefore, the arterial lumen diameter is usually measured with the leading edge-to-leading edge method (*i.e.*, the distance between the vessel far-wall interface between the lumen and intima and the near-wall interface between the adventitia and media). This method, however, might overestimate the arterial lumen diameter and arterial compliance because it excludes the near wall IMT. This constitutes a limitation of the measurement of arterial lumen diameter and compliance.

The delimitation of the population examined in this study to female subjects should be noted, because there may be gender effects on age-related changes in arterial properties. For instance, a recent study (*34*) indicated that brachial artery diameter increased with age, an effect that was more pronounced in females than in males. Additionally, as a result of arterial dilation, brachial artery compliance increased in females, but not in males. Therefore, it is reasonable to question whether the phenomenon we observed in the present

study also occurs in males. At this point, little is known about the precise mechanisms underlying the gender difference in age-induced alteration of arterial wall properties, and further studies will be necessary.

In conclusion, we sought to determine the influence of age-related carotid arterial enlargement on arterial compliance in postmenopausal females. In spite of age-related increases in carotid blood pressure and/or arterial stiffness, there was no significant age-related reduction in carotid arterial compliance among the postmenopausal female groups. A stepwise analysis indicated that age and carotid lumen diameter were two of the strongest determinants of arterial compliance, suggesting that the enlargement of arterial lumen diameter might compensate for the age-related increase in arterial stiffness, and limit the deterioration of the buffering capacity of the central artery in normotensive postmenopausal females.

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