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Large brachial and common carotid artery diameter in postmenopausal women with carotid atherosclerosis

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Abstract

Background and purpose: It is recognized that arteries can enlarge to compensate atherosclerosis. The role of diameter enlargement of unaffected arteries is not well known. We hypothesized that brachial and common carotid arteries diameters were larger in subjects with carotid atherosclerosis compared to subjects without these lesions.

Methods: We measured diameters in the common carotid and brachial arteries. Intimal medial thickness (IMT) of carotid arteries and carotid atherosclerosis were also evaluated using ultrasound in 83 cases and 83 disease-free control subjects.

Results: Common carotid and brachial diameter was greater in cases (subjects with carotid atherosclerosis) than controls (subjects without carotid atherosclerosis) after adjustment for confounding variables ($P < 0.02$). Common carotid diameter was also larger in individuals with greater IMT ($P < 0.0001$), whereas brachial artery diameter was not. Subjects with more than one carotid plaque had larger arterial diameters than those with one or without plaques.

Conclusions: Common carotid and brachial artery diameters are both larger in cases than controls. This result suggests that vascular remodeling is a systemic process and not only a local response to atherosclerosis. The relationship between diameters and burden of disease could also suggest a link between vascular remodeling and severity of disease. Finally, if confirmed in prospective studies, brachial artery diameter could help to identify subjects at high cardiovascular risk. At least in postmenopausal women.

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A growing body of evidence suggests that arteries can modify their diameter in response to a variety of stimuli, including hemodynamic changes, inflammation and injury [1]. This process, defined as vascular remodeling, is potentially important in atherosclerosis since the enlargement aim to compensate for atherosclerotic lesions, preserving, in this way, lumen diameter and blood flow [2–5]. Moreover, it seems that, sometimes, arterial compensation during development of subclinical atherosclerosis may influence the clinical presentation of vascular disease [6]. Glagov et

al. [2] demonstrated the compensatory remodeling effect in autopsy specimens of the left main coronary artery suggesting that adaptive enlargement could effectively preserve lumen area until atherosclerosis overcame the arterial compensatory response. Advances in high resolution noninvasive B-mode ultrasound have allowed the possibility of assessing carotid artery remodeling in vivo and to establish a positive relationship between carotid artery diameter and intimal medial thickness (IMT) in healthy subjects [3]. This finding has been confirmed in longitudinal studies [4]. However, the role of arterial remodeling in undiseased arteries of other vascular bed remains poorly understood. Data on women with chest pain suggested an association of lumen area of brachial artery

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with coronary artery disease [7]. On the basis of these data, it was postulated that brachial artery diameter could predict coronary artery disease [7]. B-mode ultrasound measures of asymptomatic carotid artery atherosclerosis are associated with prevalent coronary heart disease [8] and allow non-invasive study of associations of arterial walls with lumen dimensions in vivo [3]. Therefore, we used B-mode ultrasound to test the hypothesis that brachial artery diameter is larger in individuals with carotid plaque compared with carotid plaque-free controls.

1. Methods

1.1. Patient population

Participants were recruited from women undergoing menopause health-screening tests in our hospital clinic for the presence of one or more cardiovascular risk factor (hyperlipidemia, hypertension, diabetes, smoking). The study consisted of 313 postmenopausal women, with a mean age of 57 years and a carotid atherosclerosis prevalence of 45%. In 250 of them, brachial artery and common carotid diameter measurements were available. Eligible case patients (carotid plaque in at least one carotid artery) and control subjects (no carotid plaque) matched for age, since the strong association between age and arterial diameters, were recruited; we excluded those cases who have no matching control subject and this leave 166 participants. All patients provided informed consent to participate in the study, and the protocol was approved by the ethic committee of University School of Medicine.

Postmenopausal status was defined as no natural menses for at least 1 year and serum FSH level more than 40 IU/l. All the participants were Caucasian and underwent collection of medical history by a standardized questionnaire administered to obtain information about current and past medication use, smoking habits and presence of cardiovascular disease; physical examination, to evaluate body mass index (BMI) calculated as weight (in kg) divided by square of height (in m²) and blood pressure measured in both arms; vascular ultrasound to evaluate extracranial carotid atherosclerosis, carotid IMT, common carotid and brachial arteries diameters and biochemical analyses. No patient had cardiovascular symptomatic disease on the basis of clinical history. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Venous blood was collected after overnight fasting into vacutainer tubes (Becton & Dickinson) and centrifuged within 4 h. Serum glucose, creatinine, total cholesterol, high density lipoprotein cholesterol and triglycerides were measured by standard laboratory techniques. Quality control was assessed daily for all determinations.

The following criteria were used to define the cardiovascular risk factors—diabetes: fasting blood glucose ≥ 126 mg/dl or antidiabetic treatment; hyperlipidemia: total cholesterol >200 mg/dl and/or triglycerides >200 mg/dl or lipid low-

ering drugs use; hypertension: systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mmHg or antihypertensive treatment; smoking: present smokers; obesity: body mass index ≥ 30 kg/m².

1.2. Ultrasound

The subjects underwent B-mode ultrasonography of the extracranial carotid arteries by use of a duplex system (a high resolution ultrasound instrument ATL, HDI 5000 with a 5- to 12-MHz linear array multifrequency transducer). All the examinations were performed by the same ultrasonographer blinded to clinical information. All patients rested in the supine position for at least 10 min before the study and were kept in this position during the procedure. ECG leads were attached to the ultrasound recorder for on-line continuous heart rate monitoring. The right and left common (CCA) and internal carotid arteries (including bifurcations) were evaluated with the head of the subjects turned away from the sonographer and the neck extended with mild rotation. The IMT, defined as the distance between the intimal–luminal interface and the medial–adventitial interface, was measured as previously described [9]. Briefly, in posterior approach and with the sound beam set perpendicular to the arterial surface, 1 cm from the bifurcation, three longitudinal measurements of IMT were completed on the right and left common carotid arteries far-wall, at sites free of any discrete plaques. The mean of the three right and left longitudinal measurements was then calculated. Plaque, detected in longitudinal and transverse planes with anterior, lateral and posterior approaches, was defined as an echogenic focal structure encroaching into the vessel lumen of at least 50% of the surrounding IMT value. Stenosis was defined as a peak systolic velocity >120 cm/s and occlusion was defined as absence of Doppler signal. According to these criteria, subjects were considered as normal if no lesion was detected (control), or having carotid atherosclerosis when a plaque, stenosis or occlusion was detected in at least one segment of common, bifurcation or internal carotid artery (cases). The coefficient variation of the methods was 3.3%. To evaluate artery diameters images were magnified, whereas depth and gain settings were set to optimize the image of the vessel wall, in particular, the media–adventitia interface (“m” line). The end-diastolic diameter of the vessel, defined as the distance between near-wall and far-wall junctions of the media and adventitia, was measured over four cardiac cycles with the use of digital callipers and the average was then calculated. Longitudinal image of the brachial artery (BA) of the non-dominant arm was obtained proximal to the antecubital fossa wherever the best ultrasound image could be obtained.

1.3. Statistical analysis

Unpaired Student’s *t*-test and one-way ANOVA were used to compare means between the groups. Data are reported as mean \pm S.D. The χ^2 -test was used to compare the preva-

Table 1
Clinical, biochemical and ultrasound characteristics in cases and controls

Characteristic	Controls (<i>n</i> = 83) average ± S.D.	Cases (<i>n</i> = 83) average ± S.D.	<i>P</i>
Age (years)	56.94 ± 5.7	56.99 ± 5.6	NS
BMI (kg/m ²)	28.41 ± 5.3	28.63 ± 5.1	NS
SBP (mmHg)	127.25 ± 15.0	132.46 ± 17.6	0.044
DBP (mmHg)	77.67 ± 8.4	79.77 ± 9.5	NS
Glycemia (mg/dl)	96.59 ± 14.4	100.90 ± 25.3	NS
Creatinine (mg/dl)	0.79 ± 0.1	0.78 ± 0.1	NS
TC (mg/dl)	239.45 ± 47.3	242.88 ± 39.6	NS
LDL-C (mg/dl)	152.13 ± 43.1	157.39 ± 36.9	NS
HDL-C (mg/dl)	65.19 ± 16.3	60.39 ± 13.9	0.050
Tryglicerides (mg/dl)	133.09 ± 74.5	164.30 ± 164.4	NS
RCCA diameter (mm)	6.86 ± 0.7	7.30 ± 0.9	0.001
LCCA diameter (mm)	6.75 ± 0.7	7.06 ± 0.9	0.018
BA diameter (mm)	3.57 ± 0.5	3.82 ± 0.5	0.003
IMT (mm)	0.66 ± 0.15	0.73 ± 0.22	0.03
Diabetes (%)	1.2	6	NS
Hyperlipidemia (%)	45	52	NS
Hypertension (%)	23	40	0.03
Smoking (%)	19	20	NS
Obesity (%)	34	32	NS
HRT users (%)	22	10	NS

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; RCCA: right common carotid artery; LCCA: left common carotid artery; BA: brachial artery; IMT: intimal medial thickness.

lence of variables among the groups. Univariate regression analysis was performed to identify risk factors for carotid atherosclerosis and for arterial diameter enlargement. Multivariate logistic-regression analysis was performed to test for confounding variables between arteries diameters and carotid atherosclerosis. The results are expressed as odds ratios. Ninety-five percent confidence intervals are reported. All reported *P* values are two-sided. Significant differences were assumed to be present at *P* < 0.05. All comparisons were performed using the statistical package SPSS 11.0 for Windows.

2. Results

Demographic, clinical, biochemical, ultrasound characteristics and prevalence of cardiovascular risk factors of the study population are shown in Table 1. Since the similar results for right and left CCA we reported only one of these results. Carotid plaque were predominantly found in carotid bifurcation or internal carotid. No stenosis or occlusion was found.

2.1. Case-control differences in arterial diameters

Right and left common carotid and brachial diameter were significantly greater in cases than controls (Table 1; *P* < 0.02). Because of difference in systolic blood pressure and HDL between cases and control we perform a logistic-regression analysis with carotid atherosclerosis as dependent variable and the relationships with arterial diameters were essentially unaffected by adjustment for these two variables (Table 2).

2.2. Association of risk factors with arterial diameters

In univariate analysis age, BMI and systolic blood pressure were significantly and directly associated with diameter similarly in cases and controls in all the three arteries (BA, right and left CCA) explored (*P* < 0.05). In subjects affected by carotid atherosclerosis glycemia was also associated to arterial diameters of all the arteries (*P* < 0.05) (data not shown). Therefore, we performed a new logistic-regression analysis to evaluate the relationship between carotid atherosclerosis and BA and CCA diameters adjusted for age, BMI, systolic blood pressure and glycemia and the positive relationship remained unchanged (data not shown).

2.3. Associations of arterial diameters with IMT

As expected CCA diameters corrected for age are strongly correlated to IMT (*P* < 0.0001); whereas brachial artery diameter was not correlated to IMT (data not shown).

Table 2
Multivariate logistic-regression analysis of predictors of carotid atherosclerosis

	OR (95% CI)	<i>P</i>
BA diameter	2.253 (1.15–4.4)	0.017
HDL-C	0.980 (0.96–1.00)	0.083
SBP	1.013 (0.99–1.03)	0.226
CCA diameter	2.062 (1.25–3.39)	0.004
HDL-C	0.985 (0.96–1.0)	0.194
SBP	1.003 (0.98–1.03)	0.799

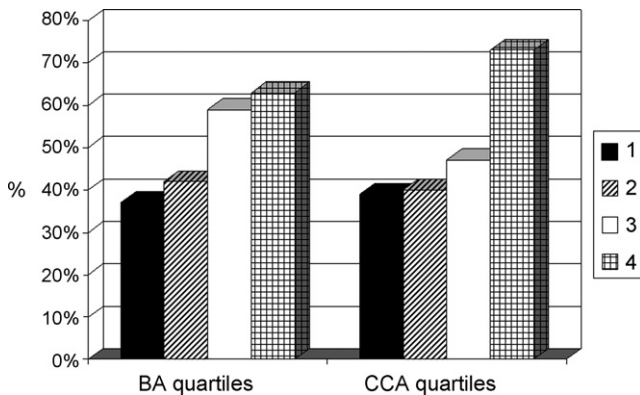


Fig. 1. Carotid atherosclerosis prevalence according quartiles of brachial artery (BA) and common carotid artery (CCA) diameters.

Table 3

Multivariate logistic-regression analysis of predictors of carotid atherosclerosis

	OR (95% CI)	P
Model 1		
BA diameter quartiles	1.490 (1.08–2.06)	0.016
HDL	0.979 (0.96–1.0)	0.066
SBP	1.012 (0.99–1.03)	0.26
Model 2		
BA diameter quartiles	1.502 (1.07–2.11)	0.020
SBP	1.015 (0.99–1.04)	0.181
Age	0.959 (0.90–1.0)	0.200
Glycemia	1.007 (0.99–1.03)	0.470
BMI	0.976 (0.91–1.04)	0.464

2.4. Prevalence of cases in population according to arterial diameters quartiles

Fig. 1 depicts the prevalence of carotid atherosclerosis in population divided in quartiles according to arterial diameters. There is increasing prevalence among quartiles ($P=0.042$). Because of probable interference of other variables we performed a regression-logistic analysis with quartile values instead that diameters value and the result was confirmed (OR 1.49, $P=0.016$) (Table 3).

2.5. Associations of arterial diameters with burden of disease

To evaluate if arterial diameters are correlated to severity of disease we separated the population in three groups: normal, with one plaque and with two or more plaques. Since no stenosis or occlusion were found, it was not possible to analyze this aspect. Analysis by ANOVA revealed that people with more burden of atherosclerosis had larger diameters

Table 4

Differences in arterial diameters between groups according burden of carotid atherosclerosis

	Normal ($n=83$) average \pm S.D.	With 1 plaque ($n=46$) average \pm S.D.	With 2+ plaques ($n=37$) average \pm S.D.	F	P
BA diameter	3.57 \pm 0.5	3.77 \pm 0.5	3.87 \pm 0.6	4.773	0.010
CCA diameter	6.86 \pm 0.7	7.12 \pm 0.7	7.52 \pm 1.1	8.468	0.000

than people affected by only one carotid plaque or normal ($P=0.01$) (Table 4).

3. Discussion

The present study describes differences in common carotid artery and brachial artery dimensions in apparent healthy postmenopausal women with and without carotid atherosclerosis. Because previous studies have described associations of age [10,11], sex [3,10–12] and physical stature [10–12] with arterial diameters, we performed a case–control study matching for age individuals of the same gender with similar BMI and all in postmenopausal condition. Therefore, these covariates did not explain for the case–control differences in arterial dimensions. Moreover, inclusion of systolic blood pressure and HDL cholesterol in multivariable models failed to explain these differences (Table 2). In animal-experimental research, various types of arteries have been shown to enlarge in response to diet-induced atherogenesis with a normal lumen preserved early in the course of disease [13,14]. Relevancy of such a process in the human vasculature was first proposed by Glagov et al. [2] and Zarins et al. [15] based on postmortem evaluations. In the late 1980s, advances in high resolution duplex ultrasound provided a basis for a noninvasive and in vivo investigation of this phenomenon. On applying this technique, Steinke et al. [4] revealed a strong relation between plaque growth and consecutive dilation of carotid arteries in a small patient-based study. Therefore, variation in the diameter has so far represented a compensatory remodeling response to local atherosclerotic lesion. Apart from this focal changes in vessel geometry at the site of progressive atherosclerosis, our study showed that others unaffected arteries, responded to active atherosclerosis in other vascular bed in terms of enlargement. This as yet unrecognized component of arterial remodeling involved brachial arteries as carotid arteries to a similar extent, emerged as independent of other potential confounders (Table 2) and appeared also correlated with the number of lesions (Table 4). On the basis of these findings, one can speculate that para/endocrine mediators affecting geometric properties are continuously released from active atherosclerotic tissue or surrounding endothelium. The biological significance of this finding expect to be clarified in future research. This is, in fact, of crucial importance in view of the fact that recent observational studies suggested that the process of outward remodeling may be associated with plaque rupture and therefore with acute coronary syndrome. Lesions responsible for unstable syndromes have, in fact, larger, softer plaques with more outward remodeling than those in stable angina, which are more fibrous

and calcified [16,17]. The aim of the present clinical study was not to explain the intimal mechanism of the relationship between arteries enlargement and carotid atherosclerosis, however, some hypotheses could be illustrated. Several evidences suggest a key role for matrix metalloproteinase (MMP) in vascular remodelling [18]. MMP belong to a family of zinc-dependent endopeptidases capable of degrading all the components of the extracellular matrix. Untimely or unbalanced MMP activity has been associated with pathological remodeling. It was demonstrated that formation of vascular lesions in a mouse blood flow cessation model is accompanied by increased gelatinolytic activity provided by MMP-2 and MMP-9 [19,20]. It was demonstrated a role for macrophages in outward arterial remodeling since the differences in vascular remodeling resulted from significantly higher levels of MMP-9 secreted by infiltrating macrophages; it was also observed a positive statistical correlation between the macrophage content of lesions and the extent of outward carotid artery remodeling in the apoE^{-/-} mouse and proposed that infiltrating macrophages may enable arterial expansive remodeling via release of MMP [18]. Specifically, pro-MMP-9, secreted constitutively by macrophages in vitro and in vivo in both experimental [21] and human [22,23] atherosclerotic lesions, could facilitate macrophage-driven geometric remodeling. Pasterkamp et al. reported increased levels of MMP-2 and MMP-9 in expansively remodeled segments of human coronary arteries compared with constrictively remodeled segments [24]. MMP-9 levels are higher in specimens of human abdominal aortic aneurysm, an extreme manifestation of expansive vascular remodelling [25], than in normal vessels [26]. Pyo et al. reported that MMP-9 knockout mice were resistant to development of experimental aortic aneurysms [27]. MMP-9 probably allows the vessel to expand breaking-down the structure of the elastic lamellae. The fact that in our study an atherosclerotic lesion in common or internal carotid is associated to larger BA diameter support this hypothesis. Moreover, future research on MMP inhibitors could find good results in control this phenomenon and contribute to stabilize atherosclerotic plaque decreasing the acute coronary syndrome.

The lack of relationship between IMT and BA diameter is not surprising since IMT and plaque measurements each represent end-organ disease in the arterial wall, but reflects different disease attributes or stages. For example, IMT is poorly correlated with traditional risk factors, except for hypertension, whereas carotid plaque is more strongly correlated to these risk factors [28]. Moreover, IMT is well correlated to left ventricular mass, whereas carotid plaque is strongly correlated to coronary atherosclerosis [29,30].

3.1. Study limitations

The present study is cross-sectional in design and used B-mode ultrasound; therefore, some caveats apply. The ultrasonographer was not blinded to the carotid atherosclerosis, when he measured the arteries diameters, and he could unwittingly

have selected a portion of brachial artery largest when he found a carotid plaque, but we did not make a particular hypothesis at the begin of the study about correlation between carotid plaque and diameters, therefore, we are confident enough about accuracy of our results. Indeed, the design of the present study does not permit us to address the temporal relationships between carotid atherosclerosis and arterial diameters; however, longitudinal studies suggest that arterial remodeling accompanies significant progression of atherosclerosis in both the carotid [4] and coronary [16] arteries. Moreover, our data probably reflect arterial dimensions in relatively early, asymptomatic carotid atherosclerosis and with progression or complication of disease, associations may differ.

4. Conclusions

Carotid atherosclerosis is associated with larger CCA e BA diameters. Although these data require confirmation in a longitudinal study, they are consistent with the concept that arterial enlargement is a systemic process occurring during atherosclerosis progression and could explains the documented association of this enlargement with symptomatic cardiovascular disease. Indeed the relationship between arterial diameters and number of lesions suggest that severity of disease is able to stimulate a major arterial diameter enlargement supporting a “dose–response” theory. Therefore, BA diameter could help to better stratify patients in the setting of cardiovascular risk at least in postmenopausal women.

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