

Carotid plaques, but not common carotid intima-media thickness, are independently associated with aortic stiffness

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Objective It has been suggested that non-invasive aortic stiffness measurements can be used as an indicator of atherosclerosis. The relationships of arterial stiffness with arterial wall hypertrophy and atherosclerosis however, have rarely been investigated in large-scale studies. The present study reports the associations of carotid arterial structure assessed by B-mode ultrasound with carotid-femoral pulse-wave velocity in hypertensive and non-hypertensive subjects.

Design and methods Free health examinations were performed on 564 subjects (age 58.2 ± 10.8 years, 31.9% of women, 53.2% of all were hypertensive). Carotid-femoral pulse-wave velocity (PWV) was used to assess aortic stiffness. Carotid ultrasound examination included measurements (at sites free of plaques) of intima-media thickness (IMT) at the common carotid arteries (CCA), CCA-lumen diameter, and assessment of atherosclerotic plaques in the extracranial carotid arteries.

Results Subjects with carotid plaques had significantly higher mean sex-adjusted values of PWV than those without carotid plaques (12.7 ± 0.2 versus 11.1 ± 0.1 m/s, $P < 0.001$). Multivariate analyses showed that this association was independent of sex, age, height, body mass index, mean blood pressure, pulse pressure, diabetes, hypercholesterolaemia and smoking habits ($P < 0.009$). PWV was positively associated with CCA-IMT

and CCA-lumen diameter in sex-adjusted analysis (partial correlation coefficients (r) were respectively 0.39 and 0.42, $P < 0.001$ for each). However, the association of PWV with CCA-IMT, but not that with CCA-lumen diameter, disappeared after further adjustment for age and blood pressure measurements (mean blood pressure and/or pulse pressure).

Conclusion This study shows that there is a differential association of PWV with CCA-IMT and carotid plaques. The nature of the independent positive association between atherosclerosis and arterial stiffness should be thoroughly investigated. *J Hypertens* 20:85–93 © 2002 Lippincott Williams & Wilkins.

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Introduction

Quantitative assessment of arterial structure and function by non-invasive methods in populations is essential for a better understanding of the pathophysiology of the vascular disease and thus, to the development of more specific prevention strategies.

B-mode ultrasound of carotid arteries is a non-invasive, valid and reproducible method of directly visualizing and assessing carotid-lumen diameter, intima-media thickness (IMT) and focal atherosclerosis (plaques) [1–3]. Non-invasive measurement of carotid-femoral pulse-wave velocity is an easy, safe and reproducible method of assessing the aortic arterial stiffness [4].

It is well known that both the ageing process and elevated blood pressure are associated with alterations in vascular structure and function [5–7]. These alterations include widening and wall thickening of large arteries and decrease in central arterial compliance (arterial stiffness) [5].

Several decades ago, it was suggested that aortic compliance measurements might be used as an indicator of atherosclerosis [8,9]. However, despite numerous investigations of the role of risk factors on the structure and function of large arteries, the relationships of arterial wall hypertrophy and atherosclerosis with arterial stiffness have rarely been the subject of specific population

studies [10,11]. Furthermore, it is not clear whether their possible inter-relationships are entirely due to their associations with common factors, particularly age and hypertension, or whether atherosclerosis process may be involved in arterial stiffening or vice versa.

In this cross-sectional study of 564 hypertensive and non-hypertensive subjects, we report the associations of carotid structure (IMT, lumen diameter and plaques) assessed by B-mode ultrasound with carotid-femoral pulse-wave velocity.

Methods

The French national health-care system permits all volunteering, working and retired persons to have a free medical examination every 5 years. The Centre d'Investigations Préventives et Cliniques (the IPC Centre) is one of the largest medical centres in France, which provides these facilities, having carried out approximately 20 000 examinations annually since 1970 for people living in the Paris area. In 1992–1993, the first subject, among those examined daily, with anti-hypertensive drug treatment ($n = 265$); the first subject with high systolic blood pressure (≥ 140 mmHg), or with high diastolic blood pressure (≥ 90 mmHg) ($n = 272$); and the first two normotensive subjects ($n = 543$), aged ≥ 18 years, were invited to participate in a study for further clinical and biological investigations of cardiovascular risk factors. Some 6 years later, these 1080 subjects were invited from November 1998 to October 1999 and 672 subjects (62.6% underwent clinical, biological, carotid ultrasound and wave pulse velocity examinations. However, ultrasound assessment of the carotid arteries could not be performed in the last 79 examined subjects for logistic reasons. A further 29 subjects who reported at the second examination a history of angina, myocardial infarction or stroke were excluded from the analysis. At the time of the first examination, there were no significant differences of cardiovascular risk factors between subjects who participated and those who did not participate in the second survey. All data shown in this report were obtained from the second examination.

The study protocol was approved by the Comité d'éthique du Centre Hospitalier Universitaire de Cochin and written informed consent was obtained from all study participants.

Ultrasonography

Ultrasound examinations were performed by two trained ultrasonographers using the Aloka SSD-650, with a transducer frequency of 7.5 MHz. Acquisition, processing and storage of B-mode images were computer-assisted with the new version of a software previously described (M'ATHS, Metris, France) [12].

The protocol, which was similar to that applied in the Ageing Vascular Study (EVA Study) [13–15], involved scanning of the common carotid arteries (CCAs), the carotid bifurcations (CBs), and the origin (first 2 cm) of the internal carotid arteries (ICA). The near and far wall of these arterial segments were scanned longitudinally and transversally to assess, at the time of the examination, the presence of plaques. The presence of plaques was defined as localized echo structures encroaching into the vessel lumen for which the distance between the media-adventitia interface and the internal side of the lesion was ≥ 1 mm. Where a plaque was found to be present, the examination was focused on that arterial site. Optimal frozen images (one longitudinal and one transversal view) showing the plaque in its greatest thickness were selected by the sonographer; frozen, transferred to a computer (PC, IBM), and digitized into 640×580 peak cells with 256 grey levels, and stored for off-line analysis. Where several plaques were found to be present on the same arterial segment (i.e., CCA or CB-ICA), the number of plaques was recorded and examination was centred on that showing the greatest encroachment into the lumen.

For IMT and lumen diameter measurements, far and near walls of the right and the left CCAs 2 to 3 cm proximal to bifurcation, were imaged. For each side, at least two optimal longitudinal images were frozen and stored for off-line analysis.

All measurements were performed by one reader (one of the sonographers). The IMT was measured at a site free of any discrete plaques along a 10 mm-long segment of the far wall of the CCA and measured as the distance between the lumen-intima interface and the media-adventitia interface using an automated edge detection algorithm. A mean of 50 measurements were automatically performed on each image (two images by side) and on each side (left and right). The mean of the right and left CCA-IMT measurements was used in the analysis. On such images, the lumen-intima interface is often more difficult to visualize on the near wall than the media-adventitia interface, and thus we chose to measure the interadventitial diameter (defined as the distance between both media-adventitia interfaces), rather than the lumen diameter. On each side, the CCA-lumen diameter was computed as the interadventitial diameter minus twice the CCA-IMT. The quantification of carotid plaques was made by measuring the IMT at the site of maximal encroachment perpendicularly to the vessel wall. The computer software did not include an automatic detection of interfaces at the site of plaque. However, the reader could be computer assisted in the identification of interfaces and placement of electronic calipers by examining the inflections of the density profile curve taken at the site of plaque. A semi-quantitative scale was used to assess the extent

and severity of plaques and graded as follows: no plaque, unilateral plaque whose thickness measured on a longitudinal view was ≤ 2 mm, unilateral plaque having thickness > 2 mm or bilateral plaques, including at least one plaque with thickness ≤ 2 mm, bilateral plaques having both thickness > 2 mm, unilateral or bilateral annular plaque.

A re-reading study was made on a random subsample of images of CCAs ($n = 100$). Mean absolute difference, coefficient of variation and correlation coefficient between repeated readings of CCA-IMT, were respectively 0.03 mm, 5.2% and 0.96. For CCA-lumen diameter, they were 0.21 mm, 8.6% and 0.83. To study the reproducibility of carotid plaque detection, 50 images of CB-ICA with plaques as defined by the sonographers and 50 images of CB-ICA without plaques were randomly chosen and re-examined by one sonographer in order to blindly assess the presence or the absence of plaques. The kappa coefficient for agreement between the two readings was 0.92.

Pulse wave velocity

Carotid-femoral pulse wave velocity (PWV) was evaluated by one physician (who did not perform the ultrasound examination) before the B-mode ultrasound examination, with two pressure probes. This method with an automatic device (Complior; Colson, Pantin, France) has been extensively analysed [16]. Briefly, two pressure waves were recorded transcutaneously at the base of the neck for the right CCA and over the right femoral artery. PWV was determined as the foot-to-foot velocity. The foot of the pressure wave was identified as the beginning point of the sharp systolic upstroke. Pulse transit time was determined as the average of 10 consecutive beats. The distance travelled by the pulse wave was measured over the body surface as the distance between the two recording sites. Aortic PWV was calculated as the ratio of distance to transit time. The validation of this automatic method and its reproducibility have been previously published, with an intra-observer repeatability coefficient of 0.93 and an interobserver reproducibility coefficient of 0.89 [16].

Blood pressure measurements

Supine blood pressure (BP) was measured, before the B-mode ultrasound examination, in the right arm using a manual sphygmomanometer. After a 10 min rest period, systolic and diastolic blood pressure (SBP and DBP) were measured three times with a 5 min interval, and the average of the last two measurements was used in the statistical analyses. Mean blood pressure (MBP) and pulse pressure (PP) were calculated using the formula [17]: $MBP = 2/3 DBP + 1/3 SBP$; $PP = SBP - DBP$.

Subjects who reported having a medical history of using

antihypertensive drugs or subjects who had $SBP \geq 160$ mmHg or $DBP \geq 95$ mmHg were considered as hypertensive.

Medical history and standard biological procedures

All participants were administered a standardized questionnaire, which provided information about demographic background, occupation, medical history, drug use and personal habits, such as cigarette consumption. Self-reported personal history of myocardial infarction or angina pectoris (personal history of CHD) was also recorded. The body mass index was computed as weight (kg) divided by height (m) squared. Subjects were classified as never smokers, former smokers, or current smokers. Total serum cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and fasting plasma glucose were also measured.

Hypercholesterolemia was defined as total cholesterol level ≥ 6.2 mmol/l (2.40 g/l) or use of lipid-lowering drugs. Subjects who reported a medical history of diabetes, use of anti-diabetic drugs or had a fasting plasma glucose level ≥ 7.0 mmol/l (1.26 g/l) were considered as diabetic.

Data analysis

Standard procedures from the Statistical Analysis System (SAS, Cary, North Carolina) were used for statistical analyses. When PWV was used as a continuous variable, its associations with CCA-IMT and CCA-lumen diameter were assessed by correlation coefficients for univariate analysis and partial correlation coefficients for multivariate analysis adjusted for conventional cardiovascular risk factors. Cardiovascular risk factors considered in the analyses were age, sex, body mass index (BMI), blood pressure (mean BP, pulse pressure, or hypertension), hypercholesterolemia, diabetes and smoking habits. Since arterial blood pressure can be divided into two components: a steady non-pulsatile component (mean blood pressure) and a pulsatile component (pulse pressure) [18], we used mean BP and pulse pressure in the multivariate analysis in order to take into account blood pressure level. The association of PWV with the presence (or absence) of carotid plaque was assessed by *t*-test for univariate analysis and analysis of covariance (ANCOVA) for multivariate analysis. Sex-specific tertiles of PWV were also used. The associations of PWV categories and parameters of arterial structure were assessed using ANCOVA and multiple logistic regression models.

Results

The main clinical characteristics of the study population at the second examination are presented in Table 1. The mean age of the 564 subjects (384 men and 180 women) was 58.2 years (± 10.8). Of the subjects, 300 (53.2%) were considered as hypertensives. Of the 161

subjects with anti-hypertensive treatment and 403 subjects without anti-hypertensive treatment at the first examination, 150 (93.2%) and 85 (21.1%), respectively were presently treated with anti-hypertensive treatment.

The B-mode ultrasound and PWV measurements are shown in Table 1. Men had higher mean values of PWV than women (11.8 ± 2.6 versus 11.1 ± 2.3 m/s, $P < 0.001$). The correlation coefficients of PWV with age, SBP, DBP, mean BP and pulse pressure were 0.48, 0.56, 0.36, 0.50 and 0.48, respectively ($P < 0.001$ for each).

The associations of PWV with cardiovascular risk factors are presented in Table 2. As expected, age and hypertension were positively associated with PWV. In contrast, neither hypercholesterolaemia nor smoking habits were significantly related to PWV (Table 2).

Associations of carotid plaques with pulse wave velocity

Subjects with carotid plaques had significantly higher mean values of PWV than those without carotid plaques (Table 3). Multivariate analyses showed that this association was independent of age, mean BP (and/or pulse pressure) and the other cardiovascular risk factors (Table 3). Figure 1 shows mean PWV in subjects with carotid plaques and in those without plaques according to age categories and hypertension status. Within each

subgroup, subjects with carotid plaques had higher mean values of PWV than those without.

The odds ratios of carotid plaques associated with sex-specific tertiles of PWV in all subjects and in subgroups are presented in Table 4. The multivariate odds ratio of carotid plaques in subjects with high values of PWV (tertile 3) compared to those with low values (tertile 1) was 2.77 (95% confidence interval: 1.37–5.51, $P < 0.001$). In the multivariate models, the substitution of SBP and DBP for mean BP and pulse pressure did not modify the results. Similar patterns of results were observed in all subgroups, although these associations were weaker in women (Tables 3 and 4).

Analyses separately repeated in anti-hypertensive treated subjects and non-treated subjects also yielded similar results. The multivariate odds ratios of carotid plaques in subjects with high values of PWV (tertile 3) compared to those with low values (tertile 1) were, respectively, 2.53 (95% confidence interval: 1.02–6.41, $P < 0.05$) in anti-hypertensive treated subjects and 2.80 (95% confidence interval: 1.24–8.34, $P < 0.01$) in non-treated subjects.

Associations of common carotid arteries intima-media thickness with pulse wave velocity

In sex-adjusted analyses (Table 5), CCA-IMT was positively associated with PWV (partial correlation coefficient (r) = 0.39, $P < 0.001$). When adjusting for sex

Table 1 Description of the population characteristics

	All $n = 564$	Men $n = 384$	Women $n = 180$	P
Age (years)	$58.2 \pm 10.8^*$	57.3 ± 10.5	60.1 ± 11.1	0.003
BMI (kg/m^2)	26.7 ± 4.0	27.2 ± 3.9	25.6 ± 4.1	0.001
Total cholesterol (mg/dl)	230.4 ± 37.9	226.7 ± 39.3	238.3 ± 33.7	0.001
Hypercholesterolaemia (%)	46.8	43.2	54.4	0.01
Triglyceride (mg/dl)	112.0 ± 109.7	125.3 ± 126.1	83.9 ± 52.8	0.001**
Glucose (mg/dl)	100.9 ± 20.1	102.4 ± 21.2	97.6 ± 17.3	0.005
Diabetes (%)	10.3	11.2	8.3	0.30
Smoking habits (%)				0.001
Never	48.4	35.7	75.6	
Ex-smokers	34.2	44.0	13.3	
Smokers	17.4	20.3	11.1	
Systolic BP (mmHg)	140.0 ± 19.9	140.4 ± 19.7	139.2 ± 20.5	0.50
Diastolic BP (mmHg)	86.1 ± 10.7	87.8 ± 11.0	82.6 ± 9.1	0.001
Mean BP (mmHg)	104.1 ± 12.4	105.3 ± 12.7	101.5 ± 11.4	0.001
Pulse pressure (mmHg)	53.9 ± 15.7	52.6 ± 14.8	56.6 ± 17.1	0.008
Hypertension (%)	53.2	55.2	48.9	0.16
Anti-hypertension treatment (%)	42.0	43.1	39.7	0.45
Duration of hypertension (years)	12.7 ± 9.0	12.3 ± 8.6	13.7 ± 10.0	0.21
CCA-IMT (mm)	0.73 ± 0.11	0.73 ± 0.11	0.74 ± 0.11	0.53
CCA-lumen diameter (mm)	6.51 ± 0.72	6.68 ± 0.70	6.14 ± 0.62	0.001
Carotid plaques (%)	28.7	32.8	20.0	0.002
Plaque severity score (%)				
Unilateral plaque ≤ 2 mm	11.5	12.2	9.9	
Unilateral plaque > 2 mm or bilateral plaques ≤ 2 mm	11.3	13.0	7.8	
Bilateral plaques > 2 mm	3.5	4.7	1.1	
Annular plaque	2.3	2.9	1.1	
Pulse wave velocity (m/s)	11.5 ± 2.5	11.8 ± 2.6	11.1 ± 2.3	0.001

BMI, body mass index; BP, blood pressure; CCA-IMT common carotid artery intima-media thickness. *Mean \pm standard deviation; **Based on log-transformation values.

Table 2 Association of pulse wave velocity with cardiovascular risk factors

	Pulse wave velocity (m/s)		
	Sex-adjusted	Sex- and MBP-adjusted	Multivariate*-adjusted
Age			
< 45 (years)	9.9 ± 0.2	10.2 ± 0.2	10.2 ± 0.2
45–59 (years)	11.4 ± 0.1	11.2 ± 0.1	11.4 ± 0.1
≥ 60 (years)	13.2 ± 0.2	12.9 ± 0.2	13.0 ± 0.2
<i>P</i>	0.001	0.001	0.001
BMI			
< 27 (kg/m ²)	11.5 ± 0.1	11.6 ± 0.1	11.6 ± 0.1
≥ 27 (kg/m ²)	11.6 ± 0.1	11.4 ± 0.1	11.4 ± 0.1
<i>P</i>	0.81	0.26	0.29
Smoking habits			
Never	11.7 ± 0.1	11.5 ± 0.1	11.6 ± 0.1
Ex-smokers	11.5 ± 0.2	11.4 ± 0.2	11.5 ± 0.1
Smokers	11.2 ± 0.2	11.5 ± 0.2	11.4 ± 0.2
<i>P</i>	0.20	0.72	0.61
Hypercholesterolaemia			
No	11.5 ± 0.1	11.5 ± 0.1	11.5 ± 0.1
Yes	11.6 ± 0.1	11.5 ± 0.1	11.6 ± 0.1
<i>P</i>	0.44	0.90	0.82
Diabetes			
No	11.5 ± 0.1	11.5 ± 0.1	11.5 ± 0.1
Yes	11.9 ± 0.3	11.9 ± 0.3	11.8 ± 0.3
<i>P</i>	0.13	0.18	0.39
Hypertension			
No	11.0 ± 0.1	–	11.0 ± 0.1
Yes	12.0 ± 0.1	–	12.0 ± 0.1
<i>P</i>	0.001	–	0.001

MBP, mean blood pressure; BMI, body mass index. Values are expressed as mean ± standard error of mean.

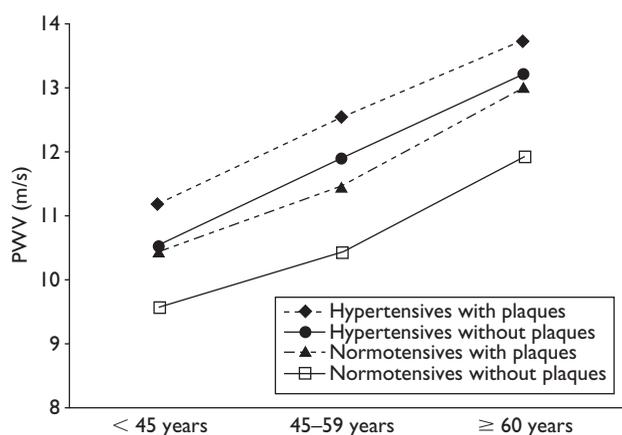
*Adjusted (where applicable) for sex, age, hypertension, body mass index, hypercholesterolaemia, diabetes and smoking habits.

Table 3 Mean values of pulse wave velocity according to the presence (or absence) of carotid plaques

	Pulse wave velocity (m/s)			
	Sex- adjusted*	Sex-, age- and MBP-adjusted	Sex-, age- and PP-adjusted	Multivariate** -adjusted
All				
Carotid plaques				
No	11.1 ± 0.1	11.3 ± 0.1	11.4 ± 0.1	11.3 ± 0.1
Yes	12.7 ± 0.2	12.0 ± 0.2	11.9 ± 0.2	11.9 ± 0.2
<i>P</i>	0.001	0.003	0.005	0.009
Men				
Carotid plaques				
No	11.2 ± 0.1	11.6 ± 0.1	11.6 ± 0.1	11.6 ± 0.1
Yes	12.9 ± 0.2	12.2 ± 0.2	12.1 ± 0.2	12.1 ± 0.2
<i>P</i>	0.001	0.006	0.009	0.01
Women				
Carotid plaques				
No	10.8 ± 0.2	10.9 ± 0.2	11.0 ± 0.1	11.0 ± 0.1
Yes	12.1 ± 0.4	11.3 ± 0.3	11.3 ± 0.3	11.3 ± 0.3
<i>P</i>	0.001	0.18	0.23	0.27
Non hypertensives				
Carotid plaques				
No	10.2 ± 0.1	10.4 ± 0.1	10.4 ± 0.1	10.4 ± 0.1
Yes	11.8 ± 0.3	11.2 ± 0.2	11.1 ± 0.2	11.1 ± 0.2
<i>P</i>	0.001	0.003	0.005	0.009
Hypertensives				
Carotid plaques				
No	12.0 ± 0.2	12.2 ± 0.2	12.3 ± 0.2	12.3 ± 0.2
Yes	13.1 ± 0.2	12.8 ± 0.2	12.7 ± 0.2	12.7 ± 0.2
<i>P</i>	0.001	0.08	0.12	0.15

MBP, mean blood pressure; PP, pulse pressure. Values are expressed as mean ± standard error of mean. *Where applicable. **Adjusted for sex (where applicable), age, mean blood pressure, pulse pressure, height, body mass index, hypercholesterolaemia, diabetes and smoking habits.

Fig. 1



Mean pulse wave velocity (PWV) in subjects with carotid plaques and in those without plaques according to age categories and hypertension status.

and age, the partial correlation coefficient became weaker but remained significant ($r = 0.12$, $P < 0.004$). The association of CCA-IMT with PWV disappeared when further adjustments for mean blood pressure ($r = 0.03$, $P = 0.47$) or pulse pressure were performed ($r = 0.02$, $P = 0.59$). Full multivariate analysis did not alter this result (Table 5). In all subgroups (according to sex and hypertension status), CCA-IMT was not associated with PWV, independently of age and blood pressure measurements and, *a fortiori*, after other cardiovascular risk factors were taken into account (Table 5).

Associations of common carotid arteries-lumen diameter with pulse wave velocity

CCA-lumen diameter was positively associated with PWV in sex-adjusted analyses ($r = 0.42$, $P < 0.001$). When age and mean blood pressure (or pulse pressure) were added to the model, correlation coefficients were attenuated but remained significant (Table 5). Similar patterns of results were observed in men and women as well as in hypertensive and non-hypertensive subjects (Table 5).

Discussion

The main findings of this large-scale study of the relationships between arterial function and structure in hypertensive and non-hypertensive subjects were as follows. First, carotid atherosclerotic plaques and CCA-lumen diameter were positively associated with aortic arterial stiffness independently of age, blood pressure (mean BP and pulse pressure) and the other conventional cardiovascular risk factors. These associations were observed in many subgroups according to gender, hypertensive status and anti-hypertensive treatment status, although the relationship of carotid plaque with arterial stiffness was more pronounced in men than in women. Second, the associations between aortic arterial stiffness and CCA-IMT were wholly explained by age and elevated blood pressure. Thus, there was a differential association of PWV with CCA-IMT and carotid atherosclerotic plaques.

In the present study, we used a methodological approach for carotid imaging that clearly differentiates between diffuse intima-media thickening and plaque. The IMT was measured in the mid- and distal portions of the common carotid artery, on a segment free of any

Table 4 Odds ratios (ORs) and (95% confidence intervals) for carotid plaques associated with sex-specific tertiles* of pulse wave velocity

Carotid plaques	Pulse wave velocity			P**
	Tertile 1 (Low)	Tertile 2	Tertile 3 (High)	
All				
Sex- and age-adjusted OR	1	2.03 (1.15-3.59)	3.01 (1.63-5.55)	0.001
Multivariate-adjusted OR***	1	1.75 (0.95-3.19)	2.77 (1.37-5.51)	0.004
Men				
Age-adjusted OR	1	2.57 (1.34-4.92)	3.44 (1.71-6.94)	0.001
Multivariate-adjusted OR***	1	2.11 (1.03-4.21)	3.09 (1.31-6.95)	0.001
Women				
Age-adjusted OR	1	0.86 (0.26-2.88)	1.77 (0.51-6.20)	0.26
Multivariate-adjusted OR***	1	0.81 (0.29-2.41)	2.01 (0.47-7.41)	0.17
Non hypertensives				
Sex- and age-adjusted OR	1	1.65 (0.74-3.70)	3.18 (1.19-8.45)	0.02
Multivariate-adjusted OR***	1	1.41 (0.56-3.41)	3.31 (1.08-9.81)	0.04
Hypertensives				
Sex- and age-adjusted OR	1	2.04 (0.86-4.84)	2.62 (1.09-6.28)	0.04
Multivariate-adjusted OR***	1	2.31 (0.91-5.60)	2.80 (1.05-7.42)	0.06

OR, odds-ratio. *Cutoff points of pulse wave velocity tertiles were 10.55 and 12.47 m/s for men, and 9.64 and 11.56 m/s for women; ** P for trend; *** Adjusted for sex (where applicable), age, mean blood pressure, pulse pressure, height, body mass index, hypercholesterolaemia, diabetes and smoking habits.

Table 5 Correlations of pulse wave velocity with β -mode ultrasound quantitative carotid measurements

	Pulse wave velocity			
	Sex-adjusted [†]	Sex-, age- and MBP-adjusted	Sex-, age- and PP-adjusted	Multivariate [‡] -adjusted
All				
CCA-IMT	0.39***	0.03	0.02	0.01
CCA-lumen diameter	0.42***	0.15***	0.14***	0.14***
Men				
CCA-IMT	0.39***	0.03	0.02	0.02
CCA-lumen diameter	0.40***	0.14*	0.13*	0.13*
Women				
CCA-IMT	0.40***	0.02	0.01	0.01
CCA-lumen diameter	0.48***	0.18*	0.18*	0.17*
Non hypertensives				
CCA-IMT	0.37***	0.03	0.02	0.02
CCA-lumen diameter	0.44***	0.24***	0.23***	0.23***
Hypertensives				
CCA-IMT	0.26***	0.02	0.02	0.02
CCA-lumen diameter	0.32***	0.13*	0.11*	0.11*

MBP, mean blood pressure; PP, pulse pressure; CCA-IMT, common carotid artery intima-media thickness. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$. [†]Where applicable; [‡]Adjusted for sex (where applicable), age, mean blood pressure, pulse pressure, height, body mass index, hypercholesterolaemia, diabetes

focal atherosclerotic lesion. We have previously reported in the EVA Study that the two types of lesions were interrelated [14] but some factors could be specifically associated with increased IMT alone or with plaques alone (such as parental history of premature death from CHD [15]).

An independent association between PWV and carotid plaques was observed in this study. Our findings corroborate the recent results of the Rotterdam Study, showing that arterial stiffness was strongly related to abdominal aortic and carotid atherosclerotic plaques [11]. In subjects with end-stage renal disease, carotid and aortic stiffness were also related to the presence and the extent of arterial calcified plaques in three arterial sites (carotid, aorta, femoral) [19]. Arterial stiffness has recently been shown to be a predictor of all-cause and cardiovascular mortality in hypertensive subjects [20] and in those with end-stage renal disease [21]. An increased arterial stiffness had also previously been reported in subjects with stroke [22] or myocardial infarction [23,24]. In the latter study, both abdominal aortic and CCA stiffness were also related to the extent of coronary atherosclerosis detected by angiography [24]. In another study, CCA stiffness in 30 hospitalized patients was closely correlated with the postmortem pathological confirmed degree of carotid atherosclerosis [25]. However, the mechanisms linking arterial stiffness to atherosclerosis are not known at present and it is not clear whether atherosclerosis results in artery wall stiffness or whether artery wall stiffness is involved in the process of atherosclerosis. Both hypotheses may be plausible, even though the first one appears to be more likely.

On the one hand, atherosclerotic changes in the arterial wall could include smooth muscle cell proliferation, deposition of lipid and accumulation of collagen, elastin and proteoglycans, without compensatory development of scar collagen [10,26]. Changes in the ratio of collagen to elastin have been known to structurally affect the elastic behaviour of the arterial wall. Thus, in addition to the primary role of ageing and hypertension, some atherogenic stimuli may be involved in arterial stiffening.

On the other hand, arterial stiffness may be involved in the atherosclerosis process. In animal studies, it has been shown that altered compliance preceded angiographically detectable early atherosclerosis in LDL-receptor deficient rabbits [27]. Furthermore, blood pressure treatment slows down the progression of carotid stenosis [28] in patients with isolated systolic hypertension (a disorder more frequently observed in the elderly and in which arterial stiffness is the major determinant). However, the mechanisms and precise role of arterial stiffness in the promotion of atherosclerosis are largely unknown.

Few studies have reported the relationships between carotid wall thickness and specific markers of arterial stiffness [10,11,29]. In the Atherosclerosis Risk in Communities (ARIC) Study [10], an increase in CCA-IMT was associated with stiffer arterial wall. This association was limited to subjects with the thickest carotid arteries (above the 90th percentile of IMT). In the Rotterdam Study, increased carotid stiffness was observed in the highest quartile of CCA-IMT [11]. In both studies, measurements of CCA-IMT were made

of the distal part of the CCA, whether a focal atherosclerotic lesion was present or not. Since the distal CCA frequently contained atheromatous plaques in the two populations [10,11], atherosclerosis rather than wall hypertrophy may be implied in the observed association between carotid wall thickness and arterial stiffness. All these results were in agreement with those of a study of 20 healthy volunteers and 90 patients with vascular disease, which showed that carotid stiffness only increased with marked wall thickening and, particularly, in segments with plaque [29].

In our study, age and hypertension appeared to be the strongest determinants of arterial stiffness. These results confirmed those of many other studies on this topic [7,30]. Age-related changes in the arterial functional properties could be attributed to the fatiguing effects of cyclic stress, acting over many decades on the inert non-living elastic fibres with subsequent stretching of the artery wall and remodelling [5]. Although these structural changes may be accelerated by hypertension [5], the increased stiffness of large arteries observed in hypertension may be due to an increase in distending pressure [31], especially in middle-aged and older hypertensive subjects [32]. The question of whether or not hypertension-associated hypertrophy and changes in structural properties may also lead to arterial stiffness could be raised. In one study, no differences of arterial stiffness, measured by luminal strain or stress-corrected luminal strain, were observed between hypertensive subjects with and without vascular hypertrophy [33]. The results of animal studies confirmed these findings and suggest that hypertension-associated hypertrophy wall does not necessarily lead to arterial stiffness and vice versa [34,35]. Lumen diameter of the common carotids was closely related to aortic arterial stiffness in our study. Since the ageing process is strongly related to both arterial widening and stiffness [7], it might have explained this association. However, after the predominant effects of age, blood pressure and the other conventional cardiovascular risk factors had been ruled out, increased lumen diameter remained independently associated with PWV. This fact suggests that other unknown and, to a lesser extent, unmeasured factors may be involved in this relationship.

Several limits to our study should be noted. No IMT measurements were made in the bifurcation-internal carotid arteries (CB-ICA) in the absence of plaques. In fact, there are large variations in the IMT according to the arterial site (ICA and CB show greater IMT than CCA [36,37]). Risk factors for atherosclerosis and CHD were more strongly associated with the ICA-IMT than with the CCA-IMT [38]. However, assessment and quantification of the IMT in the ICA and CB are far more difficult for various technical and methodological

reasons (tortuosity, proximity to the mandible, reproducibility, etc.) [37]. We used carotid-femoral PWV, which is related to the square root of the elasticity modulus [39], as a marker of aortic stiffness. The PWV was determined from foot-to-foot transit time. This fact eliminates the influence of wave reflections [40] and the eventual presence of carotid or femoral plaques will not affect the reliability of the transit time. This non-invasive superficial measurement allows only an estimate of the distance travelled by the pulse and accurate measurements of the distance are only obtained by invasive procedures assessing local change in the diameter of the aortic wall during the cardiac cycle [41]. We did adjust for BMI and height in the multivariate analyses, since body build (weight and height) may have influenced the accuracy of the carotid-femoral PWV. Our results were obtained from an observational population-based study. The interrelationships between the arterial structure and function should be complementarily investigated by the use of other research techniques and methods, which are currently beyond reach of epidemiological investigations.

In conclusion, this study suggests that carotid atherosclerotic plaques, but not diffuse intima-media thickening, are positively associated with PWV, independent of conventional cardiovascular risk factors. The nature of the association between atherosclerosis and arterial stiffness remains unclear and should be thoroughly investigated. In order to identify high-risk subjects, future prospective studies are also needed to determine which of the following is the best predictor of cardiovascular events: BP, CCA-IMT, carotid plaques, or PWV?

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