



HAL
open science

Distension of the carotid artery and risk of coronary events: the three-city study.

Nathalie Leone, Pierre Ducimetière, Jérôme Gariépy, Dominique Courbon, Christophe Tzourio, Jean-François Dartigues, Karen A. Ritchie, Annick Alperovitch, Philippe Amouyel, Michel E. Safar, et al.

► **To cite this version:**

Nathalie Leone, Pierre Ducimetière, Jérôme Gariépy, Dominique Courbon, Christophe Tzourio, et al.. Distension of the carotid artery and risk of coronary events: the three-city study.. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2008, 28 (7), pp.1392-7. 10.1161/ATVBAHA.108.164582 . inserm-00274798

HAL Id: inserm-00274798

<https://inserm.hal.science/inserm-00274798>

Submitted on 20 Oct 2008

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distension of the carotid artery and risk of coronary events-

The Three-City study

Nathalie Leone MD, Pierre Ducimetière PhD, Jérôme Gariépy MD,

Dominique Courbon MS, Christophe Tzourio MD PhD, Jean-François Dartigues MD,

Karen Ritchie PhD, Annick Alperovitch MD, Philippe Amouyel MD PhD, Michel E.

Safar MD, Mahmoud Zureik MD PhD

INSERM U700 (NL, DC, MZ), Paris; Cardiovascular Preventive Medicine, Broussais Hospital (JG), Paris; INSERM U780 (PD), U708 (CT, AA), Paris; INSERM U593 (JFD), Bordeaux; INSERM U888 (KR), Montpellier; INSERM U744 (PA), Lille; Center for Diagnostic, Hôtel-Dieu Hospital (MES), Paris

Correspondence to Nathalie Leone, MD

INSERM U700, Faculté de Médecine Xavier Bichat

16 rue Henri Huchard, BP 416

75018 Paris, France

Phone : +33 (0)1 57 27 75 70

Fax : +33 (0)1 57 27 75 51

E-mail: nathalie.leone@inserm.fr

Abstract word count: 200 - Manuscript word count: 5591

Tables: 3 – Figures: 1

Journal Subject Heads: [3] [8] [115] [144] [150]

Abstract

Objective. Arterial mechanical properties are of growing interest in the understanding of cardiovascular disease development. We aimed to determine the predictive value of carotid wall mechanics on coronary heart disease (CHD) in the Three-City study.

Methods and Results. At baseline, 3337 participants aged ≥ 65 years underwent a carotid B-mode ultrasonography. During a median follow-up of 43.4 months, 128 CHD occurred. Increased carotid distension (relative stroke change in lumen diameter) was significantly associated with CHD risk. Comparison of subjects in tertile 3 vs. those in tertile 1 (reference) showed a hazard ratio (HR) of 1.80 (95% CI, 1.17 to 2.75). Controlling for various confounders including age, heart rate, brachial or carotid pulse pressure and common carotid intima-media thickness, did not alter the association between carotid distension and CHD with a HR of 1.79 (95% CI, 1.12 to 2.86; tertile 3 vs. tertile 1). Brachial and carotid pulse pressures were also independently associated with CHD. No association was found between CHD and carotid distensibility coefficient, cross-sectional compliance coefficient, Young's elastic modulus or β stiffness index.

Conclusions. In the elderly, increased carotid distension was independently predictive of CHD. This simple and non-invasive parameter might be of particular interest for cardiovascular risk assessment.

Key Words: mechanics, carotid arteries, coronary disease, aging, ultrasonics

Condensed abstract

Relationship between B-mode ultrasound measurements of carotid wall mechanics and coronary events was investigated in a large scale population-based cohort study in the elderly. We showed that carotid distension, the stroke change in lumen diameter, was positively and independently predictive of coronary heart disease.

Studies of mechanical properties of large arteries¹ have led to the development of novel arterial parameters predicting cardiovascular events and leading to more appropriate interventions at both the individual and population level.² Most epidemiological findings on this topic have been based on systemic or regional measurements of arterial stiffness.³ In the elderly increased brachial pulse pressure (PP) or aortic pulse wave velocity have been shown to be independent predictors of cardiovascular risk.⁴⁻⁶ Because the arteries are quite heterogeneous in terms of structure and function and because this heterogeneity increases markedly with age,⁷ many studies of the aorta and of the common carotid artery (CCA) have been performed. Reports have shown that the CCA can be investigated non-invasively, using ultrasound techniques, with a high degree of resolution and reproducibility.⁸ However, very few prospective studies have addressed the association between carotid wall hemodynamics and cardiovascular disease risk.^{5, 9-13} Carotid wall mechanics have been mostly analyzed by the use of arterial stiffness indices, i.e. local stress to strain ratios: distensibility coefficient (DC), cross-sectional compliance coefficient (CC), Peterson elastic modulus, Young's elastic modulus (E_{inc}) or β stiffness index.^{14, 15} Such parameters incorporating central blood pressure are thus difficult to measure. Additionally to stiffness indices, hemodynamical properties of carotid artery might be appreciated by its distension, i.e. the systolic-diastolic expansion of the artery, during the cardiac cycle in response to local pulsatile stress. Carotid distension, can be estimated simply, non-invasively with a high reproducibility^{16, 17} and as its measurement does not incorporate PP, this mechanical parameter might be of particular interest.

Furthermore, the predictive value of carotid distension on cardiovascular disease risk in population is largely unknown, especially in the elderly. We thus used a large population-based cohort, the Three-City (3C) study, to determine whether carotid wall mechanics, carotid distension in particular, could demonstrate predictive value for coronary heart disease (CHD) in the elderly.

Methods

Subjects and study design

The design of the 3C study as well as the detailed baseline characteristics of the participants have been reported elsewhere.¹⁸ The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre, and each participant signed an informed consent. Briefly, between 1999 and 2001, 9294 community-dwelling aged ≥ 65 years were recruited from the electoral rolls of 3 French cities (Bordeaux, Dijon and Montpellier). A baseline ultrasound examination of the carotid arteries was proposed to participants aged ≤ 85 years who were able to come to the examination centers (N=8883, 95.5%). Due to logistic concerns this examination was not proposed during the last 6 months of subject recruitment, and was finally performed on 6584 subjects (74.1%). Estimation of carotid wall mechanics was provided by a special protocol introduced between December 1999 and December 2000, and thus proposed to the 4674 subjects who underwent the ultrasonography during this period (Figure 1). Carotid wall mechanics could be performed in 75.5% of these participants (N=3529). Compared with participants included during this period but without carotid wall mechanics measurements (N=1145), these subjects were somewhat younger (73.2 ± 4.7 vs. 73.7 ± 4.7 years; $P=0.005$), with slightly lower diastolic blood pressure (DBP) (81.7 ± 10.7 vs. 82.4 ± 11.6

mmHg, $P=0.02$) and lower heart rate (69.6 ± 10.6 vs. 70.9 ± 10.9 bpm, $P<0.001$). No difference was observed regarding center, CCA intima-media thickness (CCA-IMT), carotid plaques or CHD occurrence. After exclusion of 98 subjects lost to follow-up (mean age: 75 ± 5.5 years, 50% men), and 94 subjects with missing data for other covariates, the study sample was based on 3337 subjects. From this population followed during a median time of 43.4 months [min-max: 1-48] a total of 128 (3.8%) CHD occurred.

Clinical and biological evaluation

Data were collected during a face-to-face interview using a standardized questionnaire administered by trained nurses. Personal history of cardiovascular disease was defined as a history of myocardial infarction, angina pectoris, coronary balloon dilatation or artery bypass, stroke, or peripheral artery disease surgery. Centralized measurements of biological parameters were performed. Diabetes was defined as previously reported.¹⁹ Brachial blood pressure was measured twice after at least 5 min of rest in a seated position with an appropriately sized cuff placed on the right arm, using a validated automatic oscillometric device²⁰ (OMRON M4; model HEM-722C, OMRON Matsusaka Corp., Kyoto, Japan). The mean of both measures was used in the analyses. Mean blood pressure (MBP) was calculated as one-third of the sum of systolic blood pressure (SBP) plus twice DBP, and PP as the difference between SBP and DBP. Hypertension was defined as a SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg and/or use of antihypertensive drugs.

Ultrasonography

The ultrasound measurements were performed according to a scanning protocol common to the three centers, with standardized central reading of scans at the Reference Reading Center (Broussais Hospital, Paris) by one trained reader as described before.¹⁹ The B-mode system (Ultramark 9 Hight Definition Imaging) with a 5 to 10-MHz probe was used at each center. The images, along with simultaneous ECG acquisition, were transmitted to an automated computer system (IôTEC™) and digitized into 640x580 peak cells gray levels for off-line analysis. The examination involved scanning of the CCAs, the carotid bifurcations, and the origin of the internal carotid arteries right and left. The presence of plaques was assessed at the time of the examination, as previously reported.¹⁹ All measurements of CCA-IMT were made off-line at a site free of any discrete plaque and analyses are based on mean CCA-IMT of the far wall for 1-cm length of both CCAs.

Longitudinal scanning of CCAs along with simultaneous ECG acquisition, allowed visualization of the lumen-intima and media-adventitia interfaces of the near and far walls, as previously published.¹⁷ When the two parallel echogenic lines were clearly visible on the monitor along at least 1-cm, a succession of images was acquired to determine the instantaneous waveform of arterial diameter. Systolic (Ds) and diastolic (Dd) diameters were determined for each cardiac cycle and defined as the average of distances between the two leading edges of far- and near-wall lumen-intima interfaces. The diameter dimension was averaged over three or four successive cardiac cycles of right and left measurements. Carotid PP was determined according to the method from Van Bortel et al²¹ and from another equation derived from our own previously published data in the elderly.²² This second method was retained to present the results, except when otherwise mentioned in the

text, please see <http://atvb.ahajournals.org>. The distension of the CCA was evaluated as the stroke change in lumen diameter, i.e. difference between Ds and Dd (ΔD) divided by Dd:

$$\text{Carotid distension} = (D_s - D_d) / D_d, \%$$

In addition to carotid diameter, carotid PP and CCA-IMT were used to estimate the DC, the CC and the E_{inc} as follows: ^{14, 15, 23}

$$DC = (2\Delta D * D_d + \Delta D^2) / (PP * D_d^2), \text{ in } 10^{-3} / \text{kPa}$$

$$CC = \pi * (2D_d * \Delta D + \Delta D^2) / 4PP, \text{ in } \text{mm}^2 / \text{kPa}$$

$$E_{inc} = D_d / (CCA-IMT * DC), \text{ in kPa}$$

The β stiffness index was defined as follows:¹⁴

$$\beta = \ln (SBP/DBP) / [(D_s - D_d) / D_d].$$

Results of inter and intra-observer reproducibility study are available online in Figure I, please see <http://atvb.ahajournals.org>.

Ascertainment of coronary events

After baseline measurements, subjects were followed-up during a period of 4 years. CHD occurrence was ascertained every two years by examining or by contacting participants (self-administered questionnaires sent to participants who could not come to the study center), by identifying hospitalizations and deaths for potential CHD during the four years. Trained physicians obtained hospital charts and recorded presenting symptoms, out-of-hospital deaths were investigated by means of death certificates and, by an interview with one or more next-of-kin and a questionnaire filled out by the patient's physician. Coroner reports or autopsy reports, when available, were obtained. A coronary event was defined as a definite hospitalized angina, a definite hospitalized myocardial infarction, a definite CHD death (I210-I219,

I251-259, I461 and R960 ICD-10 codes) or a definite coronary balloon dilatation or artery bypass. If a patient had multiple events, the first was used in the analysis.

Statistical analysis

Carotid distension, DC, CC, E_{inc} , β stiffness index, as well as carotid and brachial PPs were analyzed as sex-specific tertiles, with the lowest tertile serving as the reference category (lowest values). Confounders independently influencing carotid distension were analyzed using a forward stepwise multiple regression. Cox proportional hazards models were used to estimate the rate ratios of CHD between the tertiles of carotid wall mechanics or brachial (or carotid) PP and for 1 standard-deviation (SD) increase in these variables. Major determinants of CHD were systematically included in the models (age, sex, body mass index (BMI), smoking status (never vs. former and current smokers), LDL cholesterol, triglycerides, diabetes mellitus, carotid plaques, cardiovascular disease history). All variables related either to carotid wall mechanics or brachial (or carotid) PP were added next (heart rate, MBP, antihypertensive drugs, lipid-lowering drugs, CCA-IMT and educational level). Linearity was tested by introducing a quadratic term in the models, which was not rejected. The proportionality assumption of Cox's model was tested by including an interaction term for follow-up time and each carotid wall mechanic or brachial (or carotid) PP separately with no evidence that the assumption was violated. Multiplicative interaction terms between carotid wall mechanics and brachial (or carotid) PP were tested. Interaction between carotid wall mechanics and brachial (or carotid) PP and their covariates was also tested in separate multivariate models. Data were analyzed with the SAS 8.02 software package (SAS Institute Inc., Cary, North Carolina, USA).

Results

Baseline characteristics of 3C participants (Table 1)

Participants were aged 73.2 ± 4.7 years, of which 39.4% were men, 74.7% had hypertension and 12.2 % had cardiovascular disease history. In general, participants in Montpellier city were younger, better educated, with lower carotid PP values and lower proportion of carotid plaques than in Bordeaux and Dijon cities (Table I, please see <http://atvb.ahajournals.org>).

Associations between confounders and carotid distension (Table 2)

In univariate analyses, age, BMI, DBP, MBP, heart rate and triglycerides were negatively linked to carotid distension. However, SBP, brachial and carotid PPs, beta-blockers, lipid lowering drugs, CCA-IMT and carotid plaques were positively associated with carotid distension (data not shown). Multivariate analysis, using forward stepwise multiple linear regression, showed that heart rate was the strongest independent predictor of carotid distension, followed by carotid PP, age, MBP, CCA-IMT, female sex and BMI. Simultaneous introduction of beta-blockers and heart rate into the model led to the loss of the association between beta-blockers and carotid distension whereas the heart rate regression coefficient remained significant (data not shown), indicating that the relation between beta-blockers and carotid distension is underlied by heart rate.

Hazard ratios (HRs) of CHD for carotid wall mechanics and brachial PP (Table 3)

CHD risk increased with increasing carotid distension up to an unadjusted HR of 1.80 (95% CI, 1.17 to 2.75) for subjects with the highest carotid distension values (tertile 3) compared with the reference group (tertile 1; P for trend=0.004). Estimate

remained statistically significant after controlling for various risk factors including heart rate, CCA-IMT and carotid plaques (tertile 3 vs. tertile 1: multiadjusted HR=2.01; 95% CI, 1.27 to 3.17). Similar results were observed after exclusion of subjects with cardiovascular disease history at baseline (n= 408 including 46 events), (tertile 3 vs. tertile 1: multi-adjusted HR=2.05; 95% CI, 1.12 to 3.75) or those using beta-blocking agents at baseline (n=549, including 37 events), (tertile 3 vs. tertile 1: multiadjusted HR=1.96; 95% CI, 1.15 to 3.34). Brachial and carotid PP were also associated with CHD risk (Table 3). Introduction of carotid distension and brachial PP in the same multi-adjusted model slightly modify their estimates for carotid distension (tertile 3 vs. tertile 1: HR=1.79; 95% CI, 1.12 to 2.86) and for brachial PP (tertile 3 vs. tertile 1: HR=1.81; 95% CI, 1.04 to 3.15). Similar results were observed for carotid distension after adjustment for carotid PP in place of brachial PP (tertile 3 vs. tertile 1: HR=1.79; 95% CI, 1.12 to 2.84). In addition, results remained unchanged by replacing brachial PP by carotid PP estimated from Van Bortel et al. (tertile 3 vs. tertile 1: HR=1.80; 95% CI, 1.13 to 2.88).

No statistically significant association was found between CHD occurrence and DC, CC, E_{inc} or β stiffness index values. Neither SBP, MBP, heart rate nor CCA-IMT values were associated with CHD risk (data not shown). DBP was negatively and independently associated with CHD events and no J curve effect was detected (data not shown). Subjects with carotid plaques at entry (45%) were at significant increased risk of CHD (multi-adjusted (model Table 3) HR=1.67; 95% CI, 1.12 to 2.49). However, no statistically significant interaction was found between these risk factors, age, sex, brachial or carotid PP, center and carotid distension on coronary risk (data not shown).

Discussion

The major finding of the 3C study, a large population-based elderly cohort, was that the increase in carotid distension was significantly predictive of CHD occurrence. This relationship was independent of age, sex, brachial and carotid PPs, heart rate, antihypertensive drugs, CCA-IMT, carotid plaques and other major cardiovascular risk factors. Confirming previous results,⁴ brachial PP was independently predictive of CHD. No association was found between CHD occurrence and carotid stiffness indices.

Since only community dwellers aged ≥ 65 years who were able to come to the study examination centers were included in our study, it is unsure to what extent our findings may be generalized to all elderly persons, notably those in institutions. Participants with carotid wall mechanics performed at baseline were somewhat younger and with lower DBP and lower heart rate compared with participants missing these measurements. But, the magnitude of such differences might not be considered as clinically relevant and no differential association was observed between the two groups regarding CHD occurrence. Subjects may have started antihypertensive medication after the baseline examination which may have affected arterial hemodynamical properties and underestimated the hazard ratios. However, in the present study, antihypertensive treatment did not appear to be a confounder when adjustment was performed. In comparing data regarding the CCA measurements of pulsatile diameter, the major difficulty is to consider which population, which device and which part of the arterial wall have been used. In our study, carotid distension values seemed somewhat higher than those previously described by others.²⁴ Geometrical carotid arterial measurements were made using B-Mode system, and according to Stadler et al.,²⁵ the mean CCA distension

amplitude from this method has been shown to be significantly larger than of the echotracking system. Nevertheless, the automated computerized B-mode ultrasound arterial diameter image has been previously validated against this method.^{17, 25} Confirming the findings of Graf et al.¹⁷, we showed high intra- and interobserver repeatability of carotid diameter measurements. In addition to the method used, differences between our measurements and those from others could be explained by the part of the arterial wall, inner or outer, chosen to estimate carotid diameter and distension values. Indeed, as observed by Segers et al.²⁶, tracking the outer wall in comparison with the inner wall as in our study, yielded higher diastolic diameter, lower absolute stroke change and lower relative stroke change. Few longitudinal studies have addressed the association between carotid hemodynamical properties and cardiovascular risk. Most of them were based on highly selected populations showing a wide variability among the values of carotid wall mechanics and contrasted results.^{5, 9-13}

Dijk et al.⁹ in a hospital-based prospective cohort study followed 2183 patients (mean age: 59.7 years) with manifest arterial disease during a mean period of 2.8 years and found no association between coronary events (n=117) and carotid distension, DC, CC, E_{inc} or β stiffness index. In the Rotterdam Study, including 2835 subjects aged ≥ 55 years and followed-up during a mean period of 4.1 years, DC was the only carotid wall mechanics parameter studied by Mattace-Raso et al.⁵, for which no association with CHD occurrence (n=101) was found. To our knowledge, only Stork et al.¹⁰ have investigated the predictive value of carotid distension on cardiovascular risk in asymptomatic individuals. After a 48 months follow-up period of 367 non-institutionalised elderly men (>70 years), the authors observed no association between carotid distension, DC, CC, β stiffness index and cardiovascular

mortality (n=28), which was mainly due to CHD (n=20). Only increased E_{inc} remained positively and independently predictive in the multivariate analysis. None of these studies estimated carotid wall hemodynamics by the use of carotid PP. In fact, it has been suggested^{5,9} that measuring carotid stiffness indices with brachial blood pressure, which is higher than carotid blood pressure in middle aged subjects,²³ might lead to an underestimation of the relation of arterial wall mechanics with CHD events. Nevertheless, the 3C study showed, in 3337 subjects ≥ 65 years, the predictive value of carotid distension and carotid PP on CHD risk, with the lack of predictive value of carotid distensibility. This finding does not exclude that other parameters, such as impedance³ or inertance²⁷ which could not be measured in this study, might act on cardiovascular risk.

The physiopathological mechanisms linking carotid distension to CHD events are to be carefully elucidated. Several hypotheses may be suggested.

First, the positive association we observed between coronary events and carotid distension but not stiffness indices might be partly explained by local PP. Stiffness indices based on blood pressure assume the hypothesis that there is a linear relationship between blood pressure and change in arterial diameter, which is not.^{1, 28} In our study, according to previous findings,²⁹ carotid PP was strongly related to coronary events. Whether local blood pressure is a cause or a consequence of carotid distension is unclear. However, the association we observed between carotid distension and coronary events was independent of carotid PP suggesting thus that the arterial wall expansion was not fully determined by the local shear and tensile stresses.

Second, the association between carotid distension and coronary events might be dominantly due to atherosclerosis. In our study, carotid distension was associated with carotid plaques. However, this parameter did not act independently on carotid distension and no statistically significant interaction was shown between them on coronary risk. Further, the association between carotid distension and coronary events was still significant after adjusting for carotid plaques, indicating that their association was not a simple consequence from atherosclerosis. Our results suggest that increased carotid distension might be less related to atherosclerosis than to arteriosclerosis, a typical feature of the aging process.

Third, carotid distension was associated with increased PP and CCA-IMT, two factors involved in vascular remodelling, with progressive thinning and fracturing of the elastic load-bearing fibers, and subsequent higher dilation of the vessel with each pulse.^{7,30} Additionally, age-induced intimal lesions and endothelial dysfunction may also participate to this vicious circle.^{1,7}

Fourth, the significant link that we observed between CHD and pulsatile diameter requires to take into account the role of aging on heart rate and the autonomic nervous system. As previously reported,^{16,31} we found that heart rate acted independently on carotid distension and was negatively related to this parameter. Heart rate reduction participates to the modification of the arterial mechanical properties, increasing markedly the hysteresis of the pressure-diameter curve and contributing to the modifications of the viscous component of the arterial wall³² and to the age-dependent baro-reflex mechanisms.³³ In this context, the role of treatment with β blockers should be considered. Beta-blocking agents did not appear to confound per se the relation between carotid distension and CHD

occurrence. However, by decreasing heart rate, beta-blocking agents may enhance the magnitude of arterial distension with possible consequences in clinical practice. It has been shown that, in hypertensive subjects, treatment with β blockers reduces adequately brachial blood pressure but does not act significantly on arterial wall structure and does not lower central systolic blood pressure as much as treatment with angiotensin-converting enzyme inhibitors or calcium antagonists.³⁴

In summary, in the 3C study, the predictive value of carotid distension on coronary events in elderly was independent of major cardiovascular risk factors, including brachial and carotid PPs. Carotid distension could be measured simply and non-invasively in large populations to identify subjects at high risk which could expand the range options for appropriate primary intervention, cardiovascular risk assessment and risk reduction strategies. Further studies are needed to better characterize the physiopathological processes underlying the association between carotid distension and CHD occurrence.

Funding Sources

The 3C study has been conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (INSERM), the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, the Institut de Santé Publique, d'Épidémiologie et de Développement (ISPED, Bordeaux), and the Ministry of Research–INSERM Programme “Cohortes et collections de données biologiques.”

Disclosures

None.

References

1. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles, 5th edn. London: Arnold, 2005.
2. Blacher J, Safar ME. Large artery stiffness and cardiovascular risk: introduction to risk assessment and new strategies. *In: Safar ME, O'Rourke MF, editors. Handbook of hypertension: arterial stiffness in hypertension. Oxford: Elsevier;2006;241-256.*
3. O'Rourke MF. Principles and definitions of arterial stiffness, wave reflections and pulse pressure amplification. *In: Safar ME, O'Rourke MF, editors. Handbook of hypertension: arterial stiffness in hypertension. Oxford: Elsevier;2006;3-19.*
4. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation.* 1999;100:354-360.
5. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation.* 2006;113:657-663.
6. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation.*2005;111:3384-3390.

7. Nichols WW, O'Rourke MF. Aging: a physical perspective. *In: Safar ME, O'Rourke MF, editors. Handbook of hypertension: arterial stiffness in hypertension. Oxford: Elsevier;2006;379-397.*
8. Crouse JR, Goldbourt U, Evans G, Pinsky J, Sharrett AR, Sorlie P, Riley W, Heiss G. Arterial enlargement in the atherosclerosis risk in communities (ARIC) cohort. In vivo quantification of carotid arterial enlargement. The ARIC Investigators. *Stroke*. 1994;25:1354-1359.
9. Dijk JM, Algra A, van der Graaf Y, Grobbee DE, Bots ML. Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. *Eur Heart J*. 2005;26:1213-1220.
10. Stork S, van den Beld AW, von Schacky C, Angermann CE, Lamberts SW, Grobbee DE, Bots ML. Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. *Circulation*. 2004;110:344-348.
11. van Dijk RA, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD. Brachial artery pulse pressure and common carotid artery diameter: mutually independent associations with mortality in subjects with a recent history of impaired glucose tolerance. *Eur J Clin Invest*. 2001;31:756-763.
12. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. *J Hypertens*. 2002;20:79-84.
13. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension*. 1998;32:570-574.

14. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens.* 2002;15:426-444.
15. Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J, Kaiser DR, Thuillez C. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. *Am J Hypertens.* 2002;15:445-452.
16. Cunha RS, Benetos A, Laurent S, Safar ME, Asmar RG. Distension capacity of the carotid artery and ambulatory blood pressure monitoring. Effects of age and hypertension. *Am J Hypertens.* 1995;8:343-352.
17. Graf S, Gariepy J, Massonneau M, Armentano RL, Mansour S, Barra JG, Simon A, Levenson J. Experimental and clinical validation of arterial diameter waveform and intimal media thickness obtained from B-mode ultrasound image processing. *Ultrasound Med Biol.* 1999;25:1353-1363.
18. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology.* 2003;22:316-325.
19. Zureik M, Gariepy J, Courbon D, Dartigues JF, Ritchie K, Tzourio C, Alperovitch A, Simon A, Ducimetiere P. Alcohol consumption and carotid artery structure in older French adults: the Three-City Study. *Stroke.* 2004;35:2770-2775.
20. Bortolotto LA, Henry O, Hanon O, Sikias P, Mourad JJ, Girerd X. Validation of two devices for self-measurement of blood pressure by elderly patients according to the revised British Hypertension Society protocol: the Omron HEM-722C and HEM-735C. *Blood Press Monit.* 1999;4:21-25.

21. Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, Vanmolkot FH, Staessen JA, Kragten JA, Vredeveld JW, Safar ME, Struijker Boudier HA, Hoeks AP. Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens.* 2001;19:1037-1044.
22. Protogerou AD, Blacher J, Mavrikakis M, Lekakis J, Safar ME. Increased pulse pressure amplification in treated hypertensive subjects with metabolic syndrome. *Am J Hypertens.* 2007;20:127-133.
23. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J.* 2006;27:2588-2605.
24. Boutouyrie P, Laurent S, Benetos A, Girerd XJ, Hoeks AP, Safar ME. Opposing effects of ageing on distal and proximal large arteries in hypertensives. *J Hypertens Suppl.* 1992;10:S87-91.
25. Stadler RW, Taylor JA, Lees RS. Comparison of B-mode, M-mode and echo-tracking methods for measurement of the arterial distension waveform. *Ultrasound Med Biol.* 1997;23:879-887.
26. Segers P, Rabben SI, De Backer J, De Sutter J, Gillebert TC, Van Bortel L, Verdonck P. Functional analysis of the common carotid artery: relative distension differences over the vessel wall measured in vivo. *J Hypertens.* 2004;22:973-981.

27. Westerhof N, Stergiopoulos N, Noble MIN. Inertance. *In: Westerhof N, Stergiopoulos N, Noble MIN, editors. Snapshots of Hemodynamics. An Aid for Clinical Research and Graduate Education. Springer US;2005;18:25-27.*
28. Lanne T, Hansen F, Mangell P, Sonesson B. Differences in mechanical properties of the common carotid artery and abdominal aorta in healthy males. *J Vasc Surg.* 1994;20:218-225.
29. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension.* 2007;50:197-203.
30. Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. *N Engl J Med.* 1994;330:1431-1438.
31. Sa Cunha R, Pannier B, Benetos A, Siche JP, London GM, Mallion JM, Safar ME. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *J Hypertens.* 1997;15:1423-1430.
32. Mangoni AA, Mircoli L, Giannattasio C, Ferrari AU, Mancia G. Heart rate-dependence of arterial distensibility in vivo. *J Hypertens.* 1996;14:897-901.
33. Monahan KD, Dinunno FA, Seals DR, Clevenger CM, Desouza CA, Tanaka H. Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance. *Am J Physiol Heart Circ Physiol.* 2001;281:H284-289.
34. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet.* 2005;366:1545-1553.

Table 1: Baseline characteristics of 3C participants (n=3337)

	Mean \pm SD or %
Age, y	73.2 \pm 4.7
Men, %	39.4
BMI, kg/m ²	25.3 \pm 3.8
Former, current smokers, %	37.1
Educational level, %	
no school or primary \pm diploma	34.0
secondary without baccalaureate degree	30.3
baccalaureate or university degree	35.7
SBP, mmHg	145.2 \pm 21.2
DBP, mmHg	81.8 \pm 10.8
MBP, mmHg	103.0 \pm 13.0
PP, mmHg	63.4 \pm 16.1
Hypertension, %	74.7
Heart rate, bpm	69.6 \pm 10.3
LDL, mmol/l	3.56 \pm 0.83
HDL, mmol/l	1.63 \pm 0.41
Triglycerides, mmol/l	1.23 \pm 0.59
Diabetes mellitus, %	9.0
Cardiovascular disease history, %	12.2
Antihypertensive drugs, %	46.2
Diuretics	13.4
Beta-blockers	16.4
Angiotensin-converting enzyme inhibitors	12.5
Calcium antagonists	11.9
Lipid lowering drugs, %	31.2
<i>Carotid artery</i>	
Systolic diameter (Ds), mm	5.77 \pm 0.81
Diastolic diameter (Dd), mm	6.31 \pm 0.88
Absolute stroke change in diameter [Ds-Dd], mm	0.53 \pm 0.15
Distension [Ds-Dd]/Dd, %	9.33 \pm 2.37
Distensibility coefficient, 10 ⁻³ /kPa	28.39 \pm 10.77
Cross sectional compliance coefficient, mm ² /kPa	0.74 \pm 0.32
Young's elastic modulus, 10 ³ /kPa	0.33 \pm 0.15
β stiffness index	5.80 \pm 1.79
Carotid PP, mmHg †	55.0 \pm 14.6
Intima-media thickness (CCA-IMT), mm	0.71 \pm 0.12
Plaques, %	45.0

Table 2: Multiple linear regression analysis with carotid distension as dependent variable

	Carotid distension ,%			Percent of explained variance ‡
	β^*	SE	<i>P</i>	
Heart rate, bpm	-0.57†	0.04	<0.001	5.64
Carotid PP, mmHg	0.65†	0.05	<0.001	4.69
Age, y	-0.41†	0.04	<0.001	2.62
MBP, mmHg	-0.45†	0.05	<0.001	2.19
CCA-IMT, mm	0.36†	0.04	<0.001	2.05
Sex (F vs. M), %	0.23	0.08	0.004	0.19
BMI, kg/m ²	-0.11†	0.04	0.005	0.18
Model's adjusted R squared			16.21	

*Regression coefficient adjusted for age, sex, center, BMI, carotid PP, MBP, heart rate and CCA-IMT.

† For 1 SD of heart rate (10.3), carotid PP (14.6), MBP (13.0), CCA-IMT (0.12), age (4.7) and BMI (3.8).

‡ Complete model's adjusted R squared minus adjusted R squared in the model without the specific factor.

Table 3: Hazard Ratios (HRs) of CHD for carotid wall mechanics and brachial PP

	No of events	HR (95% CI)	
		Unadjusted	Multadjusted †
Carotid distension,% For 1 SD* (2.37)	128	1.19 (1.01-1.41)	1.25 (1.05-1.48)
Tertile 1	33	1 reference	1 reference
Tertile 2	36	1.07 (0.67-1.73)	1.12 (0.69-1.82)
Tertile 3	59	1.80 (1.17-2.75)	2.01 (1.27-3.17)
Carotid distensibility coefficient, 10⁻³/kPa For 1 SD (10.77)	128	0.91 (0.75-1.10)	1.03 (0.84-1.26)
Tertile 1	46	1	1
Tertile 2	40	0.83 (0.54-1.28)	1.02 (0.65-1.58)
Tertile 3	42	0.88 (0.58-1.33)	1.17 (0.72-1.91)
Carotid cross-sectional compliance coefficient, mm²/kPa For 1 SD (0.32)	128	1.03 (0.88-1.20)	0.92 (0.76-1.13)
Tertile 1	42	1	1
Tertile 2	49	1.12 (0.74-1.70)	1.18 (0.77-1.81)
Tertile 3	37	0.84 (0.54-1.30)	0.86 (0.53-1.41)
Carotid Young's elastic modulus, 10³/kPa For 1 SD (0.15)	128	1.20 (1.04-1.39)	1.03 (0.86-1.23)
Tertile 1	45	1	1
Tertile 2	36	0.80 (0.52-1.24)	0.70 (0.44-1.11)
Tertile 3	47	1.08 (0.72-1.63)	0.78 (0.47-1.28)
Carotid β stiffness index For 1 SD (1.79)	128	1.15 (0.98-1.34)	1.06 (0.90-1.25)
Tertile 1	41	1	1
Tertile 2	42	1.03 (0.67-1.58)	0.95 (0.61-1.47)
Tertile 3	45	1.12 (0.73-1.71)	0.93 (0.59-1.45)
Carotid PP, mmHg For 1 SD (14.6)	128	1.37 (1.17 - 1.60)	1.39 (1.13 - 1.73)
Tertile 1	27	1	1
Tertile 2	44	1.65 (1.02 - 2.67)	1.61 (0.98 - 2.65)
Tertile 3	57	2.20 (1.39 - 3.48)	2.15 (1.24 - 3.70)
Brachial PP, mmHg For 1 SD (16.1)	128	1.43 (1.22-1.67)	1.39 (1.12-1.73)
Tertile 1	28	1	1
Tertile 2	43	1.56 (0.97-2.52)	1.53 (0.94-2.51)
Tertile 3	57	2.16 (1.38-3.40)	2.09 (1.21-3.59)

* HR per 1 standard deviation increase.

† Model adjusted for age, sex, center, smoking status, BMI, MBP, heart rate, antihypertensive drugs, LDL cholesterol, log triglycerides, lipid lowering drugs, diabetes mellitus, cardiovascular diseases history, CCA-IMT, carotid plaques and educational level.