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Association Between Arterial Stiffness and Atherosclerosis The Rotterdam Study

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Background and Purpose—Studies of the association between arterial stiffness and atherosclerosis are contradictory. We studied stiffness of the aorta and the common carotid artery in relation to several indicators of atherosclerosis.

Methods—This study was conducted within the Rotterdam Study in >3000 elderly subjects aged 60 to 101 years. Aortic stiffness was assessed by measuring carotid-femoral pulse wave velocity, and common carotid artery stiffness was assessed by measuring common carotid distensibility. Atherosclerosis was assessed by common carotid intima-media thickness, plaques in the carotid artery and in the aorta, and the presence of peripheral arterial disease. Data were analyzed by ANCOVA with adjustment for age, sex, mean arterial pressure, and heart rate.

Results—Both aortic and common carotid artery stiffness were found to have a strong positive association with common carotid intima-media thickness, severity of plaques in the carotid artery, and severity of plaques in the aorta (P for trend <0.01 for all associations). Subjects with peripheral arterial disease had significantly increased aortic stiffness ($P=0.001$) and borderline significantly increased common carotid artery stiffness ($P=0.08$) compared with subjects without peripheral arterial disease. Results were similar after additional adjustment for cardiovascular risk factors and after exclusion of subjects with prevalent cardiovascular disease.

Conclusions—This population-based study shows that arterial stiffness is strongly associated with atherosclerosis at various sites in the vascular tree. (*Stroke*. 2001;32:454-460.)

Key Words: aorta ■ atherosclerosis ■ blood flow velocity ■ carotid arteries ■ ultrasonics

Accurate noninvasive methods to measure arterial stiffness have recently become available and are relatively easy to perform.¹⁻⁴ Results from several small studies have suggested that subjects with cardiovascular disease have increased arterial stiffness compared with subjects without cardiovascular disease.⁵⁻⁸ Arterial stiffness has also been shown to be a predictor of all-cause and cardiovascular mortality in subjects with end-stage renal disease.^{9,10} The association between arterial stiffness and cardiovascular disease may be explained by an increase in pulse pressure following increased arterial stiffness or through an association between arterial stiffness and atherosclerosis. Studies examining the association between arterial stiffness and atherosclerosis have reported conflicting results. Some studies found a relation between arterial stiffness and atherosclerosis,¹¹⁻¹³ but others could not demonstrate such a relation.¹⁴⁻¹⁷ Most of the studies were performed in small groups of selected subjects and investigated the association between

arterial stiffness and atherosclerosis in only one vessel bed. The objective of the present study was to examine the association between arterial stiffness and atherosclerosis at different sites in the arterial tree in a large group of unselected, nonhospitalized subjects. Arterial stiffness was assessed in the aorta by measuring carotid-femoral pulse wave velocity (PWV) and was assessed in the common carotid artery by measuring the distensibility coefficient (DC). As indicators of atherosclerosis we used common carotid intima-media thickness, presence of plaques in the carotid artery and in the abdominal aorta, and presence of peripheral arterial disease.

Subjects and Methods

Study Population

The Rotterdam Study is a population-based cohort study that seeks to assess the occurrence of and risk factors for chronic diseases in the elderly. The rationale and design of the Rotterdam Study have been

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described in detail elsewhere.¹⁸ The baseline measurements were performed during 1990–1993. The third follow-up examination phase took place during 1997–1999. The Medical Ethics Committee of Erasmus University approved the study, and written informed consent was obtained from all participants.

Cardiovascular Disease and Risk Factors

Information on cardiovascular risk factors was collected during the third follow-up examination. Information on current health status, medical history, drug use, and smoking behavior was obtained with the use of a computerized questionnaire during a home interview. At the research center, blood pressure was measured twice, with the subject in a sitting position, at the right arm with a random zero sphygmomanometer. The average of the 2 measurements was used in the analyses. Height and weight were measured while the subject was wearing lightweight clothes and no shoes. Body mass index (BMI) (weight/height²) was calculated. Serum total cholesterol and HDL cholesterol were determined by an automatic enzymatic procedure (Boehringer Mannheim Systems). Serum glucose was determined by the hexokinase method (Boehringer Mannheim Systems). Diabetes mellitus was defined as a history of diabetes mellitus and/or the use of blood glucose-lowering medication and/or a fasting serum glucose level ≥ 7.0 mmol/L.¹⁹

Prevalent cardiovascular disease was defined as a history of myocardial infarction or stroke. Information on cardiovascular disease at the baseline examination of the Rotterdam Study was assessed during a home interview. A history of myocardial infarction and stroke was confirmed by reviewing the medical records from the general practitioner and/or medical specialist or by ECG. From baseline onward, occurrence of myocardial infarction or stroke was reported by general practitioners in the research area (85% of the cohort) by means of a computerized system. Research physicians verified all information by checking patient records of the general practitioner. The general practitioners outside the research area (15%) were visited once a year by research physicians to check patient records. In addition, discharge reports and letters of medical specialists were obtained for hospitalized patients.

Indicators of Atherosclerosis

The indicators of atherosclerosis used in this analyses were measured at the third examination phase, except the presence of calcified plaques in the abdominal aorta, which was determined during the second examination phase during 1993–1995.

Intima-media thickness was measured by recording ultrasonographic images of both the left and right carotid artery with a 7.5-MHz linear array transducer (ATL UltraMark IV, Advanced Technology Laboratories). The lumen-intima interface and the media-adventitia interface of the near and far walls of the distal common carotid artery were measured offline. The protocol has been described in detail elsewhere.^{20,21} The common carotid intima-media thickness was determined as the average of near and far wall measurements of both left and right sides.

The presence of plaques in the carotid artery was assessed by evaluating the ultrasonographic images of the common, internal, and bifurcation sites of the carotid artery for the presence of atherosclerotic lesions. Plaques were defined as a focal widening relative to adjacent segments, with protrusion into the lumen composed of either only calcified deposits or a combination of calcified and noncalcified material. No attempt was made to quantify the size of the lesions. A total carotid plaque score was defined by summation of the presence of plaques at far and near walls of left and right sides at 3 locations (maximum score of 12). Severity was graded as no plaques (score 0), mild plaques (score 1 to 4), moderate plaques (score 5 to 8), and severe plaques (score 9 to 12).

Atherosclerosis of the abdominal aorta was determined with a lateral x-ray of the lumbar spine (T12–S1), on which the presence of calcified deposits was determined. Calcified plaques were considered present when linear densities were clearly visible in an area parallel and anterior to the lumbar spine (L1–L4).²² Severity was graded from 0 (no calcified plaques) to 5 (aorta outlined with calcified plaques) according to length of affected area. Subsequently,

subjects were classified into having no (grade 0), mild (grade 1), moderate (grades 2 and 3), or severe (grades 4 and 5) atherosclerosis of the abdominal aorta.

The presence of peripheral arterial disease was assessed by the ankle-brachial pressure index, which is the ratio of the systolic blood pressure at the ankle to the average systolic blood pressure at the right arm. Systolic blood pressure of the posterior tibial artery at both left and right ankles was measured with an 8-MHz continuous-wave Doppler probe (Huntleigh 500 D, Huntleigh Technology) and a random zero sphygmomanometer with the subject in supine position.²³ The ankle-brachial pressure index was calculated for both ankles. In agreement with the approach followed by Fowkes et al,²⁴ we used the lowest ankle-brachial pressure index in either leg to determine presence of peripheral arterial disease. Peripheral arterial disease was considered present when the ankle-brachial pressure index in either leg was < 0.9 .

Reproducibility was evaluated for assessment of common carotid intima-media thickness and for assessment of atherosclerosis of the abdominal aorta. The intraclass correlation coefficient for assessment of common carotid intima-media thickness was 0.74. The percentage of agreement and the weighted κ statistic for assessment of aortic atherosclerosis were 0.75 and 0.77, respectively.

Arterial Stiffness

Aortic and common carotid artery stiffness were measured during the third examination phase with subjects in the supine position. Before measurement of PWV, blood pressure was measured twice with a sphygmomanometer after 5 minutes of rest, and the mean was taken as the subject's reading. Mean arterial pressure (MAP) was calculated by the following formula: diastolic blood pressure + $1/3 \times$ (systolic blood pressure – diastolic blood pressure). Carotid-femoral PWV was assessed with an automatic device (Complior, Colson)⁴ that assessed the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid artery and the femoral artery. The distance traveled by the pulse wave between the carotid artery and the femoral artery was measured over the surface of the body with a tape measure. PWV was calculated as the ratio between the distance traveled by the pulse wave and the foot-to-foot time delay and expressed in meters per second. The average of at least 10 successive measurements, to cover a complete respiratory cycle, was used in the analyses.

Common carotid distensibility was assessed with the subject's head tilted slightly to the contralateral side. The vessel wall motion of the right common carotid artery was measured by means of a duplex scanner (Ultramark IV, ATL) connected to a vessel wall movement detector system. The details of this technique have been described elsewhere.^{1,25} After 5 minutes of rest, a region at 1.5 cm proximal to the origin of the bulb of the carotid artery was identified by B-mode ultrasonography. The displacement of the arterial walls was obtained by processing the radio frequency signals originating from 2 selected sample volumes positioned over the anterior and posterior walls. The end-diastolic diameter (D), the absolute stroke change in diameter during systole (ΔD), and the relative stroke change in diameter [$(\Delta D)/D$] were computed as the mean of 4 cardiac cycles of 3 successive recordings. Blood pressure was measured twice with a Dinamap automatic blood pressure recorder, and the mean was taken as the subject's reading. Pulse pressure (ΔP) was calculated as the difference between systolic and diastolic blood pressure. MAP was calculated with the same formula as described for measurement of PWV. The cross-sectional arterial wall DC was calculated according to the following equation²⁶: $DC = (2\Delta D/D)/\Delta P$ ($10^{-3}/\text{kPa}$). In the present study measurements were restricted to the right side to save time. In previous studies no differences could be detected between arterial wall properties of the right and left common carotid artery (S.K. Samijo, unpublished data, 1997). A reproducibility study in 47 subjects showed an intraclass correlation coefficient of 0.80 for both carotid-femoral PWV and common carotid DC.

Population for Analysis

Of 4024 subjects eligible for a physical examination in the third examination phase, carotid-femoral PWV was measured in 3550 subjects, and common carotid distensibility was measured in 3098 subjects. Missing information on PWV or common carotid distensibility was almost entirely due to logistic reasons. Of 3550 subjects with a measurement of PWV, 69 subjects (1.9%) were excluded from the analyses because the variation between the successive PWV measurements was >10% or <10 successive measurements were made, leaving 3481 subjects for analyses. All subjects with a measurement of common carotid distensibility were included in the analyses. Of all subjects with a PWV measurement, 47% had information on carotid intima-media thickness, 87% had information on carotid plaques, 93% had information on plaques in the aorta, and 96% had information on presence of peripheral arterial disease. Of all subjects with a measurement of the DC, 53% had information on carotid intima-media thickness, 91% had information on carotid plaques, 92% had information on plaques in the aorta, and 96% had information on presence of peripheral arterial disease. Missing information on indicators of atherosclerosis was due to logistic reasons. The large number of subjects with missing information on carotid intima-media thickness was due to leeway in the offline analysis of ultrasonographic images.

Statistical Analysis

Mean PWV adjusted for age, sex, MAP, and heart rate was calculated per quartile of the continuous indicators of atherosclerosis or per category of the categorical indicators of atherosclerosis with ANCOVA. Analogously, mean DC adjusted for age, sex, MAP, and heart rate was calculated per quartile of the continuous indicators of atherosclerosis or per category of the categorical indicators of atherosclerosis. A test for trend was performed with multiple linear regression analysis, with the quartiles or categories of the different indicators of atherosclerosis as ordinal variables. Analyses were repeated after exclusion of subjects with prevalent cardiovascular disease and in strata of sex. Next, the associations were examined with multiple linear regression analysis with PWV or DC as dependent variable and the different indicators of atherosclerosis as independent variables, adjusted for age, sex, MAP, heart rate, and several cardiovascular risk factors (BMI, total cholesterol, HDL cholesterol, serum glucose, smoking, and diabetes mellitus). We also examined the association between aortic stiffness and common carotid artery stiffness with multiple linear regression analyses with DC as dependent and PWV as the independent variable and, additionally, by calculating the correlation between PWV and DC. All analyses were performed with the use of SPSS 8.0 statistical package for Windows 95 (SPSS Inc).

Results

Table 1 presents the baseline characteristics of the study population. Levels of cardiovascular risk factors were in the high normal range, as expected in a general population of elderly subjects. Mean values of PWV per quartile or per category of the indicators of atherosclerosis, adjusted for age, sex, MAP, and heart rate, are shown in Figure 1. PWV consistently increased with increasing common carotid intima-media thickness, plaques in the carotid artery, and plaques in the aorta (P for trend <0.01 for all 3 associations). Presence of peripheral arterial disease was associated with a significantly increased PWV compared with absence of peripheral arterial disease (mean difference in PWV between subjects with and without peripheral arterial disease, 0.40 m/s [95% CI, 0.17 to 0.63]). The associations of PWV with all indicators of atherosclerosis were positive. Mean values of the common carotid DC per quartile or per category of the indicators of atherosclerosis, adjusted for age, sex, MAP, and heart rate, are shown in Figure 2. The DC consistently

TABLE 1. Characteristics of the Study Population

| Characteristic | Value |
|---------------------------------|-------------|
| Age, y | 72 (60–101) |
| Men* | 58% |
| Systolic blood pressure, mm Hg | 143 (21) |
| Diastolic blood pressure, mm Hg | 75 (11) |
| Heart rate, bpm | 70 (11) |
| Total cholesterol, mmol/L | 5.8 (1.0) |
| HDL cholesterol, mmol/L | 1.4 (0.4) |
| BMI, kg/m ² | 26.8 (4.0) |
| Diabetes* | 12% |
| Smoking* | |
| Current | 16% |
| Former | 50% |
| Never | 34% |
| PWV, m/s | 13.5 (3.0) |
| DC, 10 ⁻³ /kPa | 10.5 (4.4) |
| Intima-media thickness, mm | 0.88 (0.16) |
| Plaques in carotid artery* | |
| No | 30.8% |
| Mild | 41.8% |
| Moderate | 24.9% |
| Severe | 2.5% |
| Calcified plaques in the aorta* | |
| No | 43.3% |
| Mild | 21.0% |
| Moderate | 30.7% |
| Severe | 5.0% |
| Peripheral arterial disease* | 18.1% |

Values are given as mean (SD), except for age, which is given as mean (range), and categorical variables, which are given as percentage.

*Categorical variables.

decreased with increasing intima-media thickness and plaques of the common carotid artery and plaques in the aorta (P for trend <0.01 for all 3 associations). Presence of peripheral arterial disease was associated with a borderline significantly decreased DC compared with absence of peripheral arterial disease (mean difference in DC (10⁻³/kPa) between subjects with and without peripheral arterial disease, -0.29 [95% CI, -0.62 to 0.03]). The associations of DC with all indicators of atherosclerosis were negative. Results were the same after exclusion of subjects with prevalent cardiovascular disease ($n=503$) and when performed in strata of sex (data not shown).

The results of the multiple linear regression analysis are shown in Table 2. Significant associations between PWV and all indicators of atherosclerosis were observed, adjusted for age, sex, MAP, heart rate, and cardiovascular risk factors. The DC was significantly associated with common carotid intima-media thickness, plaques in the carotid artery, and plaques in the aorta and borderline significantly associated with presence of peripheral arterial disease ($P=0.09$), after adjustment for age, sex, MAP, heart rate, and cardiovascular risk factors.

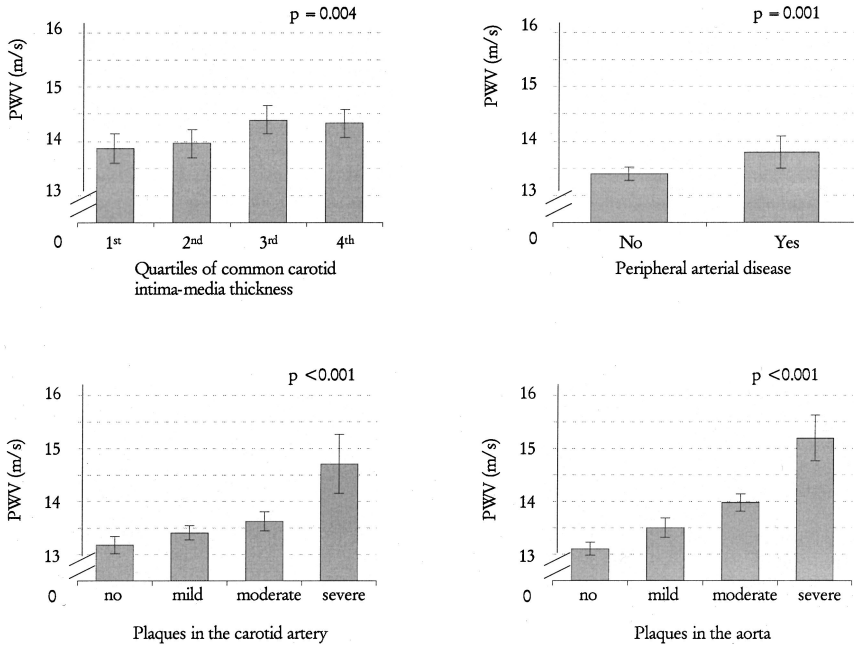


Figure 1. Mean PWV per quartile of common carotid intima-media thickness and per category of presence of peripheral arterial disease, plaques in the carotid artery, and plaques in the aorta, adjusted for age, sex, MAP, and heart rate in elderly subjects of the Rotterdam Study. Bars indicate 95% CI; probability value indicate *P* for trend, except for peripheral arterial disease, in which the *P*-value indicates *P* for difference between the groups.

A quadratic relationship was found between DC and PWV: $DC = 27.4 - 1.9 \times (PWV) + 0.04 \times (PWV)^2$ [*P* total model ≤ 0.001]. The correlation between DC and PWV was -0.41 ($P < 0.001$).

Discussion

The objective of this population-based study was to examine arterial stiffness in relation to atherosclerosis at different sites in the arterial tree. We found aortic stiffness to be strongly associated with common carotid intima-media thickness, plaques in the carotid artery and in the aorta, and presence of peripheral arterial disease. Common carotid artery stiffness was strongly associated with all indicators of atherosclerosis

except for a borderline significant association with peripheral arterial disease. Results were similar after additional adjustment for cardiovascular risk factors and after exclusion of subjects with prevalent cardiovascular disease.

Some aspects of this study need to be discussed. First, we use several noninvasive measures as indicators of atherosclerosis. Intima-media thickness and plaques in the common carotid artery have been shown to be adequate indicators of atherosclerosis of the carotid artery.^{27–29} Radiographically detected calcifications in the aorta correlate well with atherosclerotic plaques observed at autopsy, and in most cases visible calcification represented advanced atherosclerosis.³⁰ Yao and colleagues³¹ compared the ankle-brachial pressure

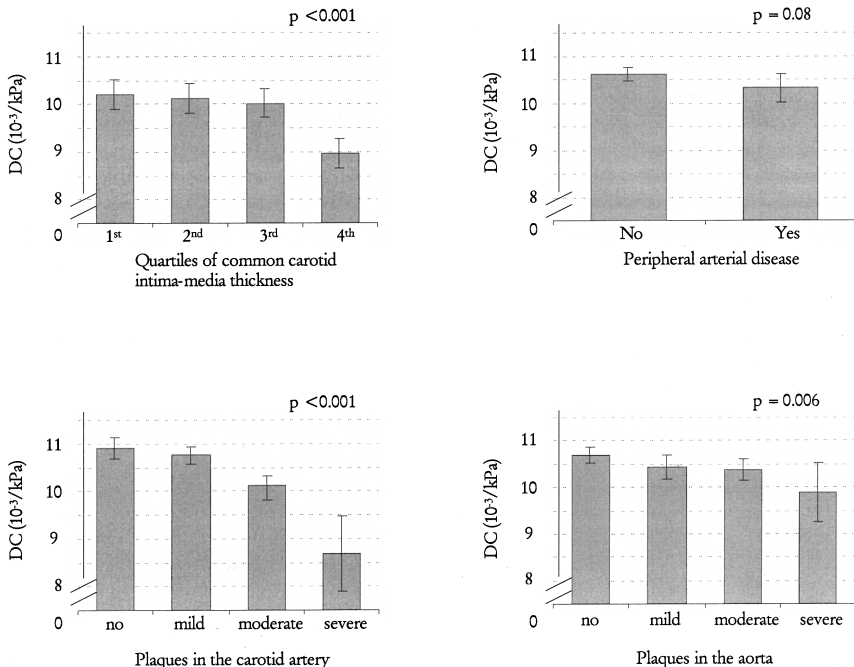


Figure 2. Mean DC per quartile of common carotid intima-media thickness and per category of presence of peripheral arterial disease, plaques in the carotid artery, and plaques in the aorta, adjusted for age, sex, MAP, and heart rate in elderly subjects of the Rotterdam Study. Bars indicate 95% CI; probability value indicate *P* for trend, except for peripheral arterial disease, in which the *P*-value indicates *P* for difference between the groups.

TABLE 2. Multiple Linear Regression (β) Coefficients and 95% CI Describing the Association* Between Aortic Stiffness and Common Carotid Stiffness and Different Indicators of Atherosclerosis in Elderly Subjects From the Rotterdam Study

| Indicator of Atherosclerosis | PWV, m/s | DC, 10 ⁻³ /kPa |
|--|--------------------|---------------------------|
| Common carotid intima-media thickness, μm | 0.96 (0.01, 1.91) | -3.12 (-4.17, -2.08) |
| Plaques in the carotid artery | | |
| Mild (vs none) | 0.20 (-0.02, 0.66) | -0.10 (-0.40, 0.21) |
| Moderate (vs none) | 0.40 (0.15, 0.66) | -0.68 (-1.05, -0.032) |
| Severe (vs none) | 1.30 (0.70, 1.90) | -2.29 (-3.15, -1.43) |
| Calcified plaques in the aorta | | |
| Mild (vs none) | 0.39 (0.17, 0.61) | -0.22 (-0.55, 0.11) |
| Moderate (vs none) | 0.80 (0.60, 1.02) | -0.25 (-0.56, 0.06) |
| Severe (vs none) | 2.06 (1.59, 2.52) | -0.80 (-1.49, -0.11) |
| Presence of peripheral arterial disease (vs absence) | 0.29 (0.05, 0.52) | -0.30 (-0.64, 0.04) |

Values are β coefficient (95% CI).

*All models adjusted for age, sex, MAP, heart rate, total cholesterol, HDL cholesterol, serum glucose, smoking, BMI, and presence of diabetes mellitus.

index with arteriography of the distal aorta and arteries of the lower extremities and demonstrated that the pressure index is a valuable and sensitive method of assessment of occlusive arterial disease. Second, some subjects were not available for measurement of arterial stiffness or atherosclerosis because they died before the third examination phase of the Rotterdam Study, because they could not participate as a result of severe illness, or because they were lost to follow-up. The unavailability of these subjects probably affected the distribution. Unfortunately, this is inevitable, especially in a population-based study among elderly subjects. Information on the different indicators of atherosclerosis was not available for every subject with a PWV measurement. This was mainly due to logistic reasons, and missing information is therefore likely to be randomly distributed over categories of severity of arterial stiffness and thus will not have introduced bias in the estimates. Third, for determining the presence of plaques in the abdominal aorta, we used x-rays from the second examination phase, which took place on average 4 years before the third examination phase in which arterial stiffness was measured. The reason for this was that x-rays made in the third examination phase were not yet evaluated for the presence of aortic plaques at the time of the present analyses. Using x-rays from the second follow-up examination phase may have led to some misclassification in severity of plaques in the aorta, but this misclassification is nondifferential with respect to arterial stiffness and thus, if present, will have led to an underestimation of the associations. Finally, BMI may have influenced determination of carotid-femoral PWV because the distance between the carotid artery and the femoral artery was measured over the body surface and therefore was dependent on body build. A high BMI can therefore result in an overestimation of carotid-femoral PWV, leading to misclassification in arterial stiffness. Since BMI is not related to atherosclerosis, this misclassification in arterial stiffness is nondifferential with respect to atherosclerosis and will thus have led to an underestimation of the association.

Previous studies on the association between arterial stiffness and atherosclerosis reported conflicting results. Nonin-

vasive measurement of distensibility of the carotid artery has been shown to be closely related to postmortem established atherosclerosis of the carotid artery.¹² The presence of atheromatous plaques in the aorta has been found to be strongly correlated with decreased aortic distensibility in subjects with various pathologies.¹³ Among hypertensive patients, those with high aortic PWV compared with those with low aortic PWV had a higher frequency of carotid artery stenosis and tended to have a higher frequency of aortic and lower limb atherosclerotic lesions.¹¹ In contrast to the above, other studies found no relation between arterial stiffness and atherosclerosis. One study found the severity of aortic atherosclerosis to be unrelated to the loss of aortic distensibility and observed a steady progression of loss of aortic distensibility with increasing age regardless of the atherosclerotic severity.¹⁴ In an ecological study, Avolio and colleagues¹⁵ found similar changes in PWV with age in populations with different prevalence of atherosclerosis and concluded that arterial distensibility is not associated with atherosclerosis. Megnien and colleagues¹⁷ found no association between aortic stiffness as determined by PWV and coronary and extracoronary atherosclerosis in a cross-sectional study of 190 asymptomatic men at risk for coronary heart disease. This study, however, comprised only a small number of subjects. The Atherosclerosis Risk in Communities (ARIC) study examined the relation between distensibility and intima-media thickness of the common carotid artery. They did not observe an association between arterial wall thickness and increased arterial stiffness, except for the thickest 10% of the artery walls.¹⁶ We found increased common carotid stiffness only in the highest quartile of intima-media thickness of the common carotid artery (Figure 2), which resembles the findings of the ARIC study, but we observed increased aortic stiffness in the upper 2 quartiles of intima-media thickness of the common carotid artery (Figure 1). The absence of a clear association between arterial stiffness and intima-media thickness in the lower 2 quartiles of intima-media thickness is in agreement with recent evidence that

suggests that intima-media thickness may only reflect atherosclerosis beyond a certain level.³²

Several possibilities for the observed association between arterial stiffness and atherosclerosis can be hypothesized. One possibility is that presence of atherosclerosis leads to stiffening of the arteries. In favor of this hypothesis is the study of Farrar and colleagues,³³ which shows an increase in PWV in cynomolgus monkeys fed an atherogenic diet and a decrease in PWV in cynomolgus monkeys fed an atherosclerosis regression diet. An alternative possibility is that increased arterial stiffness leads to vessel wall damage and atherosclerosis. Without the shock-absorbing capacity, the stiff arterial wall may be subjected to increased intraluminal stress on impact of increased pulsatile pressure.³⁴ A third possibility is that both mechanisms apply and that atherosclerosis is not only a consequence of arterial stiffness but may by itself, in advanced stages, also increase arterial stiffness. This would result in a self-perpetuating, reinforcing process. A final possibility is that arterial stiffness and atherosclerosis are independent processes that frequently occur at similar sites in the artery without the existence of a causal relationship. Future long-term longitudinal studies, preferably starting in young subjects, will be needed to elucidate the temporal relationship between arterial stiffness and atherosclerosis.

The strong association of aortic stiffness with atherosclerosis at various sites of the arterial tree suggests that aortic stiffness can be used as an indicator of generalized atherosclerosis. Whether this also holds for common carotid artery stiffness is less clear since common carotid artery stiffness was associated with carotid and aortic atherosclerosis but not clearly with the presence of peripheral arterial disease. Possibly, assessment of atherosclerosis in the abdominal aorta was more accurate than assessment of atherosclerosis of the peripheral arteries, which was assessed by a proxy.

Stiffening of the arterial tree leads to an increased systolic blood pressure and simultaneously a decreased diastolic blood pressure, resulting in wide pulse pressure.³⁵ The increased systolic blood pressure has a negative effect on the heart due to an increased workload, while a reduced diastolic blood pressure may limit coronary perfusion. These effects may explain the association between arterial stiffness and myocardial infarction, as observed in cross-sectional studies.^{36,37} Recent evidence shows that a wide pulse pressure is also a strong risk factor for stroke,^{38,39} and a cross-sectional study showed a relation between arterial stiffness and stroke.⁷ These results suggest that arterial stiffness may be a risk factor for cardiovascular diseases like stroke and myocardial infarction, which needs confirmation in prospective studies. The strong association between arterial stiffness and atherosclerosis observed in our study may provide an additional explanation for the association between arterial stiffness and cardiovascular disease. Future longitudinal studies concerning the association between arterial stiffness and cardiovascular disease must determine whether arterial stiffness is a risk factor for cardiovascular disease, independent of its association with atherosclerosis.

In conclusion, the results of this population-based study in elderly subjects suggest that arterial stiffness is associated with atherosclerosis at various sites in the arterial tree.

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References

1. Hoeks AP, Brands PJ, Smeets FA, Reneman RS. Assessment of the distensibility of superficial arteries. *Ultrasound Med Biol.* 1990;16:121–128.
2. Riley WA, Barnes RW, Evans GW, Burke GL. Ultrasonic measurement of the elastic modulus of the common carotid artery: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke.* 1992;23:952–956.
3. Lehmann ED. Elastic properties of the aorta. *Lancet.* 1993;342:1417.
4. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. *Hypertension.* 1995;26:485–490.
5. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction: a noninvasive method to predict severity of coronary atherosclerosis. *Circulation.* 1989;80:78–86.
6. Dart AM, Lacombe F, Yeoh JK, Cameron JD, Jennings GL, Laufer E, Esmore DS. Aortic distensibility in patients with isolated hypercholesterolaemia, coronary artery disease, or cardiac transplant. *Lancet.* 1991;338:270–273.
7. Lehmann ED, Hopkins KD, Jones RL, Rudd AG, Gosling RG. Aortic distensibility in patients with cerebrovascular disease. *Clin Sci (Colch).* 1995;89:247–253.
8. Gatzka CD, Cameron JD, Kingwell BA, Dart AM. Relation between coronary artery disease, aortic stiffness, and left ventricular structure in a population sample. *Hypertension.* 1998;32:575–578.
9. 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.
10. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation.* 1999;99:2434–2439.
11. Maarek B, Simon AC, Levenson J, Pithois-Merli I, Bouthier J. Heterogeneity of the atherosclerotic process in systemic hypertension poorly controlled by drug treatment. *Am J Cardiol.* 1987;59:414–417.
12. Wada T, Kodaira K, Fujishiro K, Maie K, Tsukiyama E, Fukumoto T, Uchida T, Yamazaki S. Correlation of ultrasound-measured common carotid artery stiffness with pathological findings. *Arterioscler Thromb.* 1994;14:479–482.
13. Athanassopoulos G, Olympos C, Foussas S, Cokkinos DV. Atheromatous plaques in the thoracic aorta are associated with decreased aortic distensibility evaluated with transesophageal echocardiography and automatic boundaries detection. *J Am Coll Cardiol.* 1994;146A:878–877. Abstract.
14. Nakashima T, Tanikawa J. A study of human aortic distensibility with relation to atherosclerosis and aging. *Angiology.* 1971;22:477–490.
15. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, MF OR. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation.* 1985;71:202–210.
16. Riley WA, Evans GW, Sharrett AR, Burke GL, Barnes RW. Variation of common carotid artery elasticity with intimal-medial thickness: the ARIC Study: Atherosclerosis Risk in Communities. *Ultrasound Med Biol.* 1997;23:157–164.
17. Megnien JL, Simon A, Denarie N, Del-Pino M, Garipey J, Segond P, Levenson J. Aortic stiffening does not predict coronary and extracoronary atherosclerosis in asymptomatic men at risk for cardiovascular disease. *Am J Hypertens.* 1998;11(pt 1):293–301.

18. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403–422.
19. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–1197.
20. Bots ML, van Meurs JCHM, Grobbee DE. Assessment of atherosclerosis: a new perspective. *J Drug Res*. 1991;16:150–154.
21. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–1437.
22. Witteman JC, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Burger H, Hofman A. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet*. 1994;343:504–507.
23. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the aging process: a review. *J Clin Epidemiol*. 1992;45:529–542.
24. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol*. 1991;20:384–392.
25. Kool MJ, van Merode T, Reneman RS, Hoeks AP, Struyker Boudier HA, Van Bortel LM. Evaluation of reproducibility of a vessel wall movement detector system for assessment of large artery properties. *Cardiovasc Res*. 1994;28:610–614.
26. Reneman RS, van Merode T, Hick P, Muyltjens AM, Hoeks AP. Age-related changes in carotid artery wall properties in men. *Ultrasound Med Biol*. 1986;12:465–471.
27. Fell G, Phillips DJ, Chikos PM, Harley JD, Thiele BL, Strandness DE Jr. Ultrasonic duplex scanning for disease of the carotid artery. *Circulation*. 1981;64:1191–1195.
28. Blankenhorn DH, Rooney JA, Curry PJ. Noninvasive assessment of atherosclerosis. *Prog Cardiovasc Dis*. 1984;26:295–307.
29. Bots ML, de Jong PT, Hofman A, Grobbee DE. Left, right, near or far wall common carotid intima-media thickness measurements: associations with cardiovascular disease and lower extremity arterial atherosclerosis. *J Clin Epidemiol*. 1997;50:801–807.
30. Hyman JB, Epstein FH. A study of the correlation between roentgenographic and post-mortem calcification of the aorta. *Am Heart J*. 1954;47:540–543.
31. Yao ST, Hobbs JT, Irvine WT. Ankle systolic pressure measurements in arterial disease affecting the lower extremities. *Br J Surg*. 1969;56:676–679.
32. Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness: adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam Study. *Stroke*. 1997;28:2442–2447.
33. Farrar DJ, Bond MG, Riley WA, Sawyer JK. Anatomic correlates of aortic pulse wave velocity and carotid artery elasticity during atherosclerosis progression and regression in monkeys. *Circulation*. 1991;83:1754–1763.
34. Demer LL. Effect of calcification on in vivo mechanical response of rabbit arteries to balloon dilation. *Circulation*. 1991;83:2083–2093.
35. London GM, Guerin AP. Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am Heart J*. 1999;138(pt 2):220–224.
36. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetiere P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension*. 1997;30:1410–1415.
37. Millar JA, Lever AF, Burke V. Pulse pressure as a risk factor for cardiovascular events in the MRC Mild Hypertension Trial. *J Hypertens*. 1999;17:1065–1072.
38. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension: prognostic information provided by pulse pressure. *Hypertension*. 1999;34:375–380.
39. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB. The role of diastolic blood pressure when treating isolated systolic hypertension. *Arch Intern Med*. 1999;159:2004–2009.