

Increased Arterial Stiffness Is Independently Related to Cerebrovascular Disease and Aneurysms of the Abdominal Aorta

The Second Manifestations of Arterial Disease (SMART) Study

J.M. Dijk, MD; Y. van der Graaf, MD, PhD; D.E. Grobbee, MD, PhD; J.D. Banga, MD, PhD; M.L. Bots, MD, PhD; on behalf of the SMART Study Group

Background—Arterial stiffness is a risk factor for stroke and myocardial infarction. We investigated whether carotid arterial stiffness is related to other localizations of manifest arterial disease.

Methods—Carotid artery stiffness was measured by ultrasonography as the change in diameter in systole relative to the diastolic diameter in patients enrolled in the Second Manifestations of Arterial Disease (SMART) Study, a cohort study among patients with manifest cardiovascular disease or cardiovascular risk factors. The first consecutive 1561 patients with manifest cardiovascular disease were classified in 4 categories: cerebrovascular disease, coronary artery disease, peripheral artery disease, or aneurysm of the abdominal aorta (AAA). Differences in arterial stiffness among the categories were studied by linear regression analyses. Patients with coronary artery disease as single diagnosis (n=482) served as reference group.

Results—Patients with cerebrovascular disease (arterial distension $-42.0 \mu\text{m}$ [95% CI, -57.2 to -26.8]) and those with an AAA ($-64.4 \mu\text{m}$ [95% CI, -84.8 to -44.0]) had an increased carotid stiffness compared with the reference group. Adjustment for confounders attenuated the relations, which remained statistically significant ($-34.2 \mu\text{m}$ [95% CI, -47.8 to -20.7] and $-33.2 \mu\text{m}$ [95% CI, -51.8 to -14.6], respectively).

Conclusion—Our study suggests that increased arterial stiffness is important in the pathophysiology of especially cerebrovascular disease and AAA. That the differences in arterial stiffness between disease categories attenuated after adjustment for important risk factors but remained significant suggests that besides being an element in the causal pathway, arterial stiffness is also a risk factor for cardiovascular disease itself. (*Stroke*. 2004;35:1642-1646.)

Key Words: cardiovascular diseases ■ cerebrovascular disorders ■ aortic aneurysm ■ carotid arteries ■ elasticity

Cardiovascular disease is the leading cause of mortality and morbidity in industrialized nations. Many cardiovascular risk factors are known, but they do not precisely predict which individuals will develop arterial disease in the future. Arterial stiffness has been shown to be a risk factor for stroke and myocardial infarction in certain populations.¹⁻³ On 1 hand, increased arterial stiffness is the result of a damaging effect on the arterial wall over time by other cardiovascular risk factors (notably age and hypertension).⁴ Thus, increased arterial stiffness can be viewed as an intermediate: a factor in the pathway between risk factors and cardiovascular disease. On the other hand, arterial stiffness is a risk factor for cardiovascular disease independent of other risk factors,¹⁻³ and a genetic basis for increased arterial stiffness is suspected.⁵ Not much is known about the relationship of arterial stiffness to localizations of manifest arterial disease, notably

localizations other than coronary artery disease or cerebrovascular disease. This is of interest because arterial stiffness may be more important in the development of manifest disease at a certain localization than at another. To further understand its pathophysiological role, we examined the relationship of arterial stiffness of the carotid artery with different localizations of manifest arterial disease. Furthermore, we determined whether this relationship can be explained by risk factors.

Patients and Methods

Study Population

We used data from patients enrolled in the Second Manifestations of Arterial Disease (SMART) Study. The SMART study is an ongoing prospective single-center cohort study in patients with manifest cardiovascular disease or cardiovascular risk factors. Starting in

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From the Julius Center for Health Sciences and Primary Care (www.juliuscenter.nl) (J.M.D., Y.v.d.G., D.E.G., M.L.B.) and the Department of Vascular Medicine (J.D.B.), University Medical Center Utrecht, Utrecht, The Netherlands.

Members of the SMART Study Group are listed in the Appendix.

Correspondence to Dr J.M. Dijk, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Huispostnummer Str 6.131, PO Box 85060, 3508 BA Utrecht, The Netherlands. E-mail j.m.dijk@jc.azu.nl

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TABLE 1. Disease Categories

Disease Category	Inclusion Diagnosis	Medical History*	Vascular Screening
Cerebrovascular disease	Cerebral ischemia	TIA	
	TIA	Stroke	
	Amaurosis fugax		
	Stroke		
	Retina infarction		
Coronary artery disease	Myocardial infarction	Myocardial infarction	
	Angina pectoris	Angina pectoris	
		CABG or PTCA	
Peripheral vascular disease	Intermittent claudication leg	Peripheral vascular disease	Resting ABP-index ≤ 0.90
	Restpain/ulcer leg	Arterial operation or PTA leg	
		Amputation leg	
Aneurysm abdominal aorta	Aneurysm abdominal aorta	Aneurysm abdominal aorta Surgery for aneurysm abdominal aorta	Aneurysm abdominal aorta†

*Ever or current diagnosis.

†Distal aortic anteroposterior diameter ≥ 3 cm or distal:proximal ratio ≥ 1.5 .

CABG indicates coronary artery bypass; PTCA, percutaneous transluminal coronary angioplasty; PTA, percutaneous transluminal angioplasty; ABP, ankle-brachial pressure.

1996, consecutive patients aged 18 to 80 years, referred to the University Medical Center Utrecht with manifest cardiovascular disease or a cardiovascular risk factor, underwent a vascular screening including a questionnaire, blood chemistry, and ultrasonography. Written informed consent was obtained from all participants. The study was approved by the medical ethics committee of the University Medical Center Utrecht. The rationale and design of the SMART study have been described in detail previously.⁶

For the current study, the data of the first consecutive 1802 patients with manifest cardiovascular disease (cerebral, coronary, or peripheral artery disease or aneurysm of the abdominal aorta [AAA]) were considered. For 149 participants, stiffness measurements were missing because of equipment failure or logistical problems. Measurements of 92 participants were excluded from the analysis: the intraindividual variance between stiffness assessments was considered out of range in 70 participants, and 22 participants had a history of carotid artery surgery. Finally, the data of 1561 patients were used in the analyses.

Measurements

Carotid Artery Stiffness

Stiffness was assessed by measurement of distension of the carotid arteries. The distension of an artery is the change in diameter in systole relative to the diastolic diameter during the cardiac cycle. Lower distension implies a stiffer artery. The displacement of the walls of the left and right common carotid artery was measured with a wall track system (Scanner 200, Pie Medical) equipped with a 7.5 MHz linear array transducer and the vessel wall movement detector system. Patients were examined in supine position, with the head turned $\approx 45^\circ$ away from the side examined. The left and right carotid arteries were examined separately. Measurements were performed in the distal common carotid artery 2 cm proximal to the origin of the carotid bulb. Details of the measurements have been described in detail previously.⁷ In short, at the right carotid artery, 5 assessments were performed. Each assessment lasted 4 seconds and comprised several cardiac cycles. First, the measured distension of the cardiac cycles within a single assessment was averaged. Next, the measurements of the 5 assessments were averaged. A similar procedure was used for the left carotid artery. The mean of the left and right carotid artery measurements was taken as distension measurement for 1 individual. The same procedure was followed for lumen diameter measurements.

Vascular Screening

Full vascular screenings were conducted on single days at the University Medical Center Utrecht. Blood samples were collected after an overnight fast. Glucose, total cholesterol, triglycerides, and high-density cholesterol (HDL-c) were measured. Low-density lipoprotein cholesterol (LDL-c) was calculated by use of Friedewald formula. Height and weight were measured without shoes and heavy clothing. Blood pressure was measured in supine position at the right brachial artery every 4 minutes during the arterial stiffness measurement, with a semiautomatic oscillometric device (Omega 1400, In Vivo Research Laboratories Inc). The left and right ankle-brachial pressure indices at rest were determined. Ultrasonography of the abdomen was performed to measure anteroposterior juxtarenal and infrarenal diameter of the aorta, and color duplex scanning of the internal carotid arteries was performed to detect carotid artery stenosis. Use of current medication and smoking pack years were derived from a questionnaire described previously.⁶

Cardiovascular Disease Categories

Participants were classified into disease categories on the basis of referral diagnosis, medical history, and findings at the cardiovascular screening. The disease categories were: cerebrovascular disease, coronary artery disease, peripheral vascular disease, and AAA. For definitions, see Table 1. A participant could be classified into more than 1 disease category. For example, a person referred for angina pectoris in whom an AAA was found during screening was classified into 2 groups: coronary artery disease and AAA.

Data Analysis

First, a linear regression model was constructed with the disease categories as independent variables and the carotid distension as dependent variable (model I). Participants with coronary artery disease served as reference group. In a second model, diastolic carotid diameter and systolic blood pressure (SBP) and diastolic blood pressure were added to model I as important determinants of distension (model II). We chose to use diastolic and SBP instead of pulse pressure or mean arterial pressure based on a higher adjusted R^2 of the linear regression model. To examine the differences in arterial stiffness as an independent risk factor, we adjusted for confounding variables by constructing a third linear regression model. The variables age, pack years, LDL-c, diabetes mellitus, and body mass index were added to model II (model III). These confounders were selected because they could reasonably have a confounding effect and appeared to alter the regression coefficients

of at least 1 of the disease categories with minimally 10% when added to the model. Sex, weight, triglycerides, HDL-cholesterol, carotid artery stenosis of $\geq 50\%$ or $\geq 70\%$, and use of antihypertensive or lipid-lowering medication appeared not to confound the associations. SBP² was added to minimize residual confounding.

Patients in the reference group had coronary artery disease as single diagnosis, whereas patients in the other disease categories could have more than 1 localization of cardiovascular disease. To be able to evaluate whether an observed difference in arterial stiffness was because of the number of localizations of disease or to the disease category itself, the analysis was repeated in the 1093 patients with only 1 localization of cardiovascular disease.

Of 189 patients with a clinical manifestation of arterial disease, information concerning 1 or more of the potential confounders was missing. In a complete case analysis, these patients cannot be included in multivariate analysis, which causes a loss of power and introduces potential bias.⁸ To reduce bias and increase statistical efficiency, missing values in the data were completed by regression imputation.⁹ With this method, a value was assigned to the missing data using regression analysis based on all available complete data.⁸

Results

Table 2 gives the general patient characteristics of the study population. Of the 1561 patients, 74% were male. Mean arterial distension was 419.6 μm (SD 144.6). Coronary artery disease was present in 753 participants and in 482 of them as single manifestation of arterial disease (reference group). Antihypertensive medication was used by 999 patients (64%), and 553 (35%) used lipid-lowering medication.

The arterial distension was significantly lower, implying a higher stiffness among those with an AAA ($-65.3 \mu\text{m}$ [95% CI, -85.4 to -45.3]) or cerebrovascular disease ($-38.9 \mu\text{m}$ [-54.1 to -23.7]) compared with the reference group (Table 3, model I). Adjustment for diastolic carotid diameter and SBP and diastolic blood pressure did not materially affect the relationships (Table 3, model II). When cardiovascular risk factors were taken into account, the distension of those with an AAA ($-34.6 \mu\text{m}$ [-53.2 to -16.0]) or cerebrovascular disease ($-29.7 \mu\text{m}$ [-43.5 to -15.8]) remained statistically significantly lower than in the reference group (Table 3, model III). The arterial distension in patients with peripheral artery disease was not significantly different from the patients with coronary artery disease.

Repeating the analysis in the 1093 patients with only 1 manifestation of arterial disease did not substantially change the findings (Table 3, model III: cerebrovascular disease [$n=52$]: $-34.4 \mu\text{m}$ [95% CI, -53.3 to -18.5]; AAA [$n=60$]: $-20.2 \mu\text{m}$ [-61.9 to 5.6]; peripheral arterial disease [$n=299$]: $-5.6 \mu\text{m}$ [-24.3 to 13.1]).

Discussion

We showed that arterial stiffness, measured in the common carotid artery, differs between localizations of manifest cardiovascular disease.

Some methodological aspects need to be addressed. First, proper adjustment for hypertension is necessary to study arterial stiffness as an independent risk factor. Adjustment for blood pressure measured at 1 point in time may not completely remove the confounding effect of a chronic exposure to elevated blood pressure. Consequently, the relationship of arterial stiffness with manifest disease may be overestimated because of residual confounding by chronic hypertension.

TABLE 2. General Characteristics of the Study Population (n=1561)

Men (%)	74
Age (years)	60.7 (10.3)
SBP (mm Hg)	141.3 (20.2)
DBP (mm Hg)	79.0 (9.8)
Diastolic diameter common carotid artery (μm)	8081 (1115)
Distension (μm)	419.6 (144.6)
Triglycerides (mmol/L)	2.1 (2.1)
LDL-c (mmol/L)	3.7 (1.0)
HDL-c (mmol/L)	1.1 (0.3)
Weight (kg)	79.1 (13.6)
Height (cm)	173 (9.0)
Body mass index (kg/m^2)	26.2 (3.8)
Cigarette pack years	23.0 (20.1)
Current smoking (%)	40
Former smoking (%)	44
Diabetes mellitus* (%)	22
Medication	
ACE inhibitor or AT1-antagonist† (%)	22
Alpha-blocking agent (%)	1
Beta-blocking agent (%)	44
Calcium antagonist (%)	24
Diuretics (%)	13
Lipid-lowering medication (%)	35
Cardiovascular disease category‡	
AAA (%)	14
Coronary artery disease (%)	52
Cerebrovascular disease (%)	32
Peripheral artery disease (%)	39
Coronary artery disease as single diagnosis (%)	31

Data are mean (SD) or %.

*Glucose-lowering medication, fasting glucose ≥ 7.0 mmol/L or nonfasting glucose ≥ 11.1 mmol/L.

†ACE inhibitor indicates angiotensin-converting enzyme inhibitor; AT1-antagonist, angiotensin II-antagonist.

‡Ever or current diagnosis, a single patient can be classified into more than one disease category.

For definitions, see Table 1.

Yet, the effect is likely to be small because the use of antihypertensive medication, probably a better marker for chronic hypertension than current blood pressure, was not related to arterial stiffness when added to the model including current blood pressure values. Second, we used the distension of the carotid arteries as a measurement of arterial stiffness instead of the more commonly used distensibility coefficient (2 [distension/diastolic diameter]/pulse pressure) as noncombined variables were preferred. Using a ratio in a model may obscure the impact of the separate variables. Instead of correcting for diastolic lumen diameter and pulse pressure by using the distensibility coefficient, we adjusted for those variables in a linear regression model. Third, blood pressure was measured at the brachial artery, whereas stiffness measurements were performed at the carotid artery. It is known that the brachial SBP may be an overestimation of the carotid

TABLE 3. Relation of Arterial Stiffness to Different Localizations of Cardiovascular Disease

Disease Category	Model I β (95% CI)	Model II β (95% CI)	Model III β (95% CI)
Cerebrovascular disease	-38.9 (-54.1 to -23.7)	-42.0 (-57.3 to -26.8)	-29.7 (-43.5 to -15.8)
AAA	-65.3 (-85.4 to -45.3)	-62.9 (-83.3 to -42.6)	-34.6 (-53.2 to -16.0)
Renal artery stenosis	-38.6 (-89.8 to 12.6)	-31.1 (-81.2 to 19.0)	-29.5 (-73.7 to 14.7)
Peripheral arterial disease	18.9 (4.4 to 33.4)	8.1 (-6.7 to 22.8)	3.9 (-9.9 to 17.9)

β indicates regression coefficient.

Model I: Unadjusted relation of arterial stiffness to different manifestations of cardiovascular disease.

Model II: Model I, additionally adjusted for diastolic diameter common carotid artery and diastolic and systolic blood pressure.

Model III: Model II, additionally adjusted for SBP², age, height, pack years, LDL-c, waist circumference, diabetes mellitus, and beta-blocking medication.

SBP because of changes in amplitude and timing of wave reflections along the arterial tree.¹⁰ Because this SBP amplification decreases with increasing arterial stiffness,¹¹ in patients with stiff arteries, the measured brachial blood pressure may resemble the blood pressure in the carotid artery better than in patients with more elastic arteries, in whom the difference may be larger. This may have caused an overestimation of the association of stiffness to disease localization. Because we adjusted for risk factor levels with special emphasis on blood pressure, and because all patients had manifest disease and thus all had relatively stiff arteries, this is not likely to have biased our results. Finally, in this study, arterial stiffness in the disease categories was not compared with the stiffness in healthy individuals. Other studies have shown that in coronary¹² and peripheral artery disease,¹³ arterial stiffness is higher than in healthy control subjects. So it is likely that in our study the groups with the most elastic arteries, the patients with coronary and peripheral artery disease, had stiffer arteries than healthy subjects. Using healthy individuals as reference group probably would not have changed the differences in stiffness between disease categories.

Arterial stiffness can be seen as an element in the causal chain: risk factor \rightarrow arterial stiffness \rightarrow manifestation of disease based on the notion that several cardiovascular risk factors have been known to increase arterial stiffness, and increased arterial stiffness is related to cardiovascular morbidity and mortality. The differences in arterial stiffness between disease categories then reflect differences in risk factors and a different effect of these risk factors on the arterial wall between disease categories. Moreover, that the differences in arterial stiffness between disease categories remained significant after adjusting for important risk factors suggests that besides being an element in the causal pathway (an intermediate), arterial stiffness is a risk factor itself. This may be the result of differences in the structure of connective tissue in the arterial wall, which partly determines the stiffness of the arterial wall and may be a result of genetic differences.^{5,14}

We found that patients with cerebrovascular disease, AAA, or a history of these diseases had a high arterial stiffness. Different explanations can be suggested. Concerning cerebral artery disease, presence of atherosclerosis in the carotid artery has been shown to alter carotid stiffness.¹⁵ Nevertheless, this does not explain the increased carotid stiffness in patients

with cerebrovascular disease in our study because adjustment for carotid artery stenosis did not change the association. Other possible explanations are more easily development of a stenosis in a stiff carotid artery or a plaque in a stiff carotid artery being more unstable than a plaque in an elastic vessel.¹⁶ Concerning AAA, formation of an aneurysm is thought to be caused by destruction of elastin in the aortic wall, causing a shift of the blood pressure load on collagen. Once the shielding effect of elastin is lost, further dilatation and rupture of the aorta depend on the physical properties of the collagen.¹⁷ A significant correlation between stiffness in an AAA and the carotid artery has been shown.¹⁸ Consequently, the increased carotid stiffness in AAA patients may reflect an increased stiffness of the abdominal aorta. This may be explained by a lower amount of elastin, a different type of collagen, or by a more detrimental effect of cardiovascular risk factors on the arterial wall in these patients.

The relatively low arterial stiffness in patients with coronary artery disease may point to a minor role of arterial stiffness in the pathophysiology of this manifestation of arterial disease. Alternatively, carotid stiffness only partly reflects total aortic stiffness (correlation coefficient 0.42),¹⁹ and our observation may be explained by a weak relationship of carotid stiffness with coronary artery disease as opposed to a strong relationship of total aortic stiffness with coronary artery disease (N.M. Popele et al, unpublished data, 2000). This suggests that the site at which arterial stiffness develops or is present is of pathophysiological importance for the type of arterial disease that develops.

Similarly, the relatively low arterial stiffness in patients with peripheral arterial disease may reflect differences in composition between the predominantly elastic carotid arteries and the more muscular peripheral arteries.²⁰

Our findings may have clinical implications because angiotensin-converting enzyme inhibitors²⁰ and advanced glycation end-product breakers²¹ have shown to effectively reduce arterial stiffness and may reduce cardiovascular morbidity.²² It is of interest to further establish the impact of these drugs on different localizations of disease, especially the disease categories with the stiffest arteries that may benefit most from this treatment.

In conclusion, the results of our study support the view that patients with cerebrovascular disease or AAA have an increased carotid stiffness compared with patients with coronary artery disease, also after adjustment for cardiovascular

risk factors. This suggests that increased arterial stiffness, measured in the carotid arteries, is important in the pathophysiology of especially cerebrovascular disease and AAA.

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Appendix

Members of the SMART Study Group (in alphabetical order): A. Algra, MD, FAHA, Julius Center for Health Sciences and Primary Care and Department of Neurology; J.D. Banga, MD, PhD, Department of Vascular Medicine; B.C. Eikelboom, MD, PhD, Department of Vascular Surgery; Y. van der Graaf, MD, PhD, Julius Center for Health Sciences and Primary Care; D.E. Grobbee, MD, PhD, Julius Center for Health Sciences and Primary Care; P.P.Th. de Jaegere, MD, PhD, Department of Cardiology; L.J. Kappelle, MD, PhD, Department of Neurology; H.A. Koomans, MD, PhD, Department of Nephrology; W.P.T.M. Mali, MD, PhD, Department of Radiology; F.L. Moll, MD, PhD, Department of Vascular Surgery; G.E.H.M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care; F.L.J. Visseren, MD, PhD, Department of Vascular Medicine; all members are from the University Medical Center Utrecht, The Netherlands.

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