Aortic stiffness is associated with atherosclerosis of the coronary arteries in older adults: the Rotterdam Study

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Objective **Aortic stiffness can lead to low diastolic blood pressure, thereby possibly limiting coronary perfusion. Therefore, the simultaneous occurrence of both aortic stiffness and coronary atherosclerosis can lead to an increased risk of subendocardial ischaemia. The aim of the present study was to investigate the association between aortic stiffness and coronary atherosclerosis.**

Methods **The study was performed in 1757 subjects of the Rotterdam Study, a population-based study of elderly individuals. Aortic stiffness was assessed by measuring carotid-femoral pulse wave velocity (PWV). Coronary atherosclerosis was assessed by measuring coronary calcification using electron beam tomography and expressed as a total calcium score. The total calcium score was log-transformed because of its skewed distribution. The association between PWV and coronary calcification was first evaluated after adjustment for age, sex, mean arterial blood pressure and heart rate.**

Results **Linear regression analyses showed that increased PWV was associated with a higher log total coronary calcium score [β-regression coefficient 0.11, 95% confidence interval (CI) 0.07–0.15]. Compared with the lowest quartile of PWV, multivariate odds ratios and corresponding 95% CI for advanced coronary calcification in the second, third and fourth highest quartiles were 1.17 (0.79–1.74), 1.58 (1.07–2.34) and 2.12 (1.40–3.20), respectively.**

Conclusions **In this large population-based study performed in elderly subjects aortic stiffness was strongly and independently associated with coronary atherosclerosis. *J Hypertens* 24:2371–2376 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Aortic stiffness can adversely affect the myocardium as increased aortic stiffness leads to an increase in aortic systolic blood pressure (SBP), thereby increasing the workload and oxygen consumption of the heart [1,2]. Furthermore, aortic diastolic blood pressure (DBP) is decreased by aortic stiffness, thereby limiting coronary perfusion [1,2]. In healthy individuals, a decreased coronary perfusion pressure can be compensated by coronary vasodilatation [3]. However, in the presence of coronary atherosclerosis, the vasodilatory reserve is limited and a decreased perfusion pressure in these circumstances can lead to decreased oxygen supply, especially the subendocardial supply [4–7]. Some data have suggested that arterial stiffness and atherosclerosis are related processes [8,9], and we have recently shown that aortic stiffness predicts cardiovascular events in older adults [10]. If arterial stiffness and coronary atherosclerosis occur together more frequently than expected by chance, this would indicate the presence of a high-risk group at increased risk of subendocardial ischaemia. One study evaluated the relationship between aortic stiffness and calcification of the coronary arteries assessed using electron beam tomography, but could not demonstrate an association [11]. However, that study comprised a small number of subjects. Other studies have shown an association between arterial stiffness and coronary atherosclerosis in patients undergoing coronary angiography [12,13]. The objective of the present study was to investigate the association between aortic stiffness and atherosclerosis of the coronary arteries, assessed by measuring coronary calcification using electron beam tomography, in a large population-based study of apparently healthy individuals.

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Methods

Study population

The Rotterdam Study is a population-based cohort study that aims at assessing the occurrence of and risk factors for chronic diseases in the elderly. The rationale and design of the Rotterdam Study have been described in detail elsewhere [14]. In March 1997, the third examination phase started. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study, and written informed consent was obtained from all participants. Measurements of both aortic stiffness and coronary calcification were available for 1757 subjects who attended the third follow-up examination, and these subjects were included in the study.

Aortic stiffness

Aortic stiffness was assessed during the third follow-up examination by measuring carotid-femoral pulse wave velocity (PWV). PWV was not measured in 12% of all subjects who attended the third examination phase, which was almost entirely caused by logistic reasons. Subjects were instructed to refrain from smoking and from taking coffee, tea, alcohol or pain medication on the day of measurement, and from taking alcohol on the day before the measurement. Carotid-femoral PWV was measured with the subject in a supine position. After 5 min rest, blood pressure was measured twice using a conventional sphygmomanometer and the mean was taken as the subject's reading. Mean arterial pressure (MAP) was calculated by the following formula: DBP + 1/3 * (SBP − DBP). Subsequently PWV was measured. The time delay between the feet of simultaneously recorded pulse waves was measured using an automatic device (Complior Artech Medicla, Pantin, France) [15]. The distance traveled by the pulse wave between the carotid artery and the femoral artery was measured over the surface of the body using a tape measure. PWV was calculated as the ratio of the distance traveled by the pulse wave and the foot-to-foot time delay and was expressed in meters per second. The average of at least 10 successive measurements, to cover a complete respiratory cycle, was used in the analyses.

Coronary atherosclerosis

Coronary atherosclerosis was assessed during the third follow-up examination by measuring coronary calcification with an Imatron C-150 EBT scanner (Imatron, South San Francisco, California, USA). All subjects under 85 years of age were invited for the measurement of coronary calcification by electron beam tomography. Subjects were placed in a supine position. The scan was obtained using a neutral, transverse position of the subject, with the single slice mode with 3 mm slice thickness, 100 ms exposure time at 130 kV and 630 mA, during electrocardiograph gating at 80% of the R–R interval in suspended inspiration. In this mode, 38 adjacent slices were obtained from the level of the root of the aorta through the entire heart. Coronary calcification was quantified off-line by encircling each area of high density in the course of an epicardial coronary artery, thus indicating a region of interest around the presumed lesion. Software, provided by AccuImage Diagnostics Corporation displays within this region of interest all pixels having Hounsfield units higher than 130. The calcium score is then obtained by multiplying the area of interest, when it was larger than 0.65 mm^2, by a factor indicating the maximum density within that area, as proposed by Agatston *et al.* [16]. As the distribution of the calcium score is highly skewed, a log transformation of the calcium score is used in the analyses, according to the following formula: log calcium score = ln (total calcium score + 1). The value of 1 was added to the total calcium score as many subjects had a total calcium score of zero. Subjects in the highest quartile of the calcium score were considered to have advanced calcification. Subjects without calcifications of the coronary arteries (9.2%) were used as the reference group.

Cardiovascular risk factors

Information on cardiovascular risk factors was collected during the third follow-up examination. Data on drug use and smoking habits were obtained during the home interview. Body mass index [weight (kg)/height^2 (m)] was calculated. Serum total cholesterol and high-density lipoprotein cholesterol values were determined using an automated enzymatic procedure (system from Boehringer Mannheim, Mannheim, Germany). Diabetes mellitus was defined as the use of blood glucose-lowering medication or a fasting serum glucose level equal to or greater than 7.0 mmol/l [17]. Hypertension was defined as a blood pressure level of 160/90 mmHg or greater or the use of antihypertensive medication. Prevalent cardiovascular disease was defined as a history of myocardial infarction or stroke. Information on cardiovascular disease was assessed during a home interview. A history of myocardial infarction and stroke was confirmed by reviewing the medical records from the general practitioner or medical specialist or by electrocardiogram. The occurrence of myocardial infarction or stroke was reported by general practitioners in the research area. Research physicians verified all information by checking patient records of the general practitioner. In addition, discharge reports and letters from medical specialists were obtained for hospitalized patients.

Measurement of atherosclerosis

Ultrasonography of both carotid arteries was performed using a 7.5-MHz linear array transducer and a duplex scanner (ATL UltraMark IV; Bothell, Washington, USA). 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 [18]. The maximum common carotid intima–media thickness (IMT) was

determined as the average of the maximum IMT of near and far wall measurements over a length of 1 cm, and the average of the left and right maximum common carotid IMT was computed.

Population for analyses

Of the 4024 subjects who underwent the physical examination of the third phase of the Rotterdam Study, aortic stiffness measured as PWV was measured in 3550 subjects, whereas coronary calcification was measured in 2013 subjects. Missing information on both measures was almost entirely caused by logistic reasons. Finally, data on PWV and coronary calcification were available for 1757 subjects who were included in the study. Data on carotid IMT were available for 1630 subjects.

Statistical analysis

We used logarithmically transformed values of the coronary calcium score to normalize the distribution of this variable. The association between arterial stiffness and coronary calcification was first investigated by linear regression analysis, with PWV as the independent variable and the log calcium score as the dependent variable. Second, logistic regression analyses were performed to calculate the odds ratio and its 95% CI for the presence of advanced coronary calcification (defined as the highest quartile of coronary calcium) by increasing quartiles of PWV. The cut-off points for quartiles of PWV were 11.3, 12.9 and 14.8 m/s. Analyses were adjusted for age, sex, MAP, heart rate (model 1). Body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking status, the use of antihypertensive medication, the use of statins and previous cardiovascular disease were also included in the model (model 2). Additional adjustment was made including measures of carotid IMT in the last model (model 3). Subsequently, analyses were conducted in strata of age, sex, diabetes mellitus, smoking, hypertension, and previous cardiovascular disease. Adjusted mean values of the log calcium score were calculated across quartiles of PWV. The association between carotid IMT and both arterial stiffness and coronary calcification was investigated by multivariate linear regression analysis, with carotid IMT as the independent variable. All analyses were performed using the SPSS 11.0 statistical package for Windows 95 (SPSS Inc., Chicago, Illinois, USA).

Results

The characteristics of the study population are presented in Table 1. The mean age of the population was 71 ± 5.6 years, 50.1% of the population were men, and 305 subjects (17.3%) had had a previous cardiovascular event. After adjustment for age, sex, MAP and heart rate, the log of the total coronary calcium score was linearly associated with PWV (β-regression coefficient 0.11, 95% CI 0.07–0.15), associations remained statistically significant after adjustment for cardiovascular risk factors and after additional adjustment for IMT (Table 2). Compared with the lowest quartile of PWV, odds ratios and corresponding 95% CI for advanced coronary calcification in the second, third and fourth quartiles were 1.17 (0.79–1.74), 1.58 (1.07–2.34) and 2.12 (1.40–3.20), respectively, in models adjusted for age, sex, cardiovascular risk factors and carotid IMT (Table 3). Figure 1 shows the adjusted mean values of the log calcium score across quartiles of PWV. In stratified analyses, associations between arterial stiffness and coronary atherosclerosis remained unchanged, only in smokers were the data inconsistent (Table 4). As reported in previous studies performed in the same cohort [9,19] we have found an association between carotid IMT and PWV (multivariate adjusted β-regression coefficient and 95% CI 2.93; 0.82–2.64) and coronary calcium (multivariate adjusted β-regression coefficient and 95% CI 1.48; 0.73–2.22).

Table 1 Characteristics of the study population ($n = 1757$)

Characteristic	
Age (years)	71 ± 5.6
Men (%)	50.1
Mean arterial blood pressure (mmHg)	107.1 ± 12
Heart rate (bpm)	74.6 ± 15.6
Body mass index (kg/m^2)	26.7 ± 3.6
Total cholesterol (mmol/l)	5.8 ± 0.9
HDL-cholesterol (mmol/l)	1.3 ± 0.4
Smoking (%)	16.9
Diabetes mellitus (%)	6.8
Previous cardiovascular disease (%)	17.3
Use of antihypertensive medication (%)	21.5
Use of statins (%)	14.8
Hypertension (%)	46.9
Carotid intima–media thickness (mm)[a]	0.87 ± 0.14
Log total calcium score	4.8 ± 2
Pulse wave velocity (m/s)	13.4 ± 2.9

HDL, High-density lipoprotein. Values are expressed as percentage or mean ± standard deviation. [a] Measures of intima–media thickness were available in 1630 subjects.

Discussion

The results of our population-based study in elderly subjects show that aortic stiffness is associated with atherosclerosis of the coronary arteries, subjects with higher aortic stiffness had significantly higher mean values of coronary calcification.

Some aspects of the study need to be discussed. First, we used coronary calcification, as detected by electron beam

Table 2 Linear regression coefficients describing the increase in log total calcium score per 1 m/s increase in pulse wave velocity

	Subjects	β Coefficient	95% CI	*P* value
Model 1	1757	0.11	0.07–0.15	< 0.001
Model 2	1757	0.09	0.03–0.11	< 0.001
Model 3	1630	0.08	0.05–0.13	< 0.001

CI, Confidence interval. Model 1: adjusted for age, sex, mean arterial blood pressure and heart rate. Model 2: as model 1 with additional adjustment for body mass index, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes mellitus, antihypertensive medication, the use of statins and previous cardiovascular disease. Model 3: as model 2 with additional adjustment for carotid intima–media thickness.

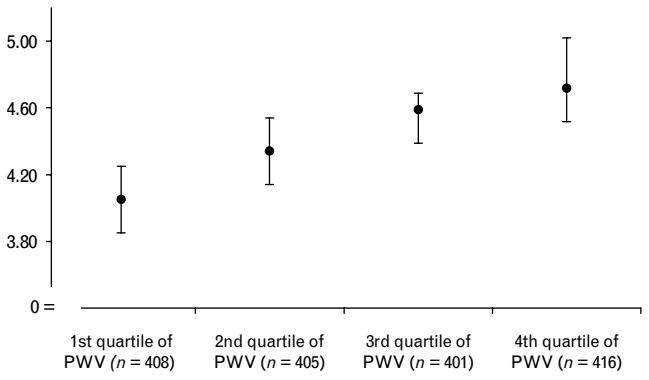
Table 3 Odds ratios of high coronary calcification by quartiles of pulse wave velocity

PWV	Model 1 OR 95% CI	Model 2 OR 95% CI	Model 3 OR 95% CI
1st Quartile	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd Quartile	1.17 (0.80–1.69)	1.06 (0.70–1.58)	1.06 (0.69–1.60)
3rd Quartile	1.58 (1.10–2.28)	1.46 (0.98–2.17)	1.39 (0.92–2.11)
4th Quartile	2.41 (1.64–3.53)	2.26 (1.49–3.43)	2.03 (1.32–3.13)

CI, Confidence interval; OR, odds ratio; PWV, pulse wave velocity. Model 1: adjusted for age, sex, mean arterial blood pressure and heart rate. Model 2: as model 1 with additional adjustment for body mass index, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes mellitus, antihypertensive medication, the use of statins and previous cardiovascular disease. Model 3: as model 2 with additional adjustment for carotid intima–media thickness.

tomography, as a measure of coronary atherosclerosis. Blankenhorn [20] summarized the evidence that coronary artery calcification occurs only at sites involved with atherosclerosis. Several studies showed that calcification is more often present in non-stenotic disease than in stenotic disease [21]. A total calcium score assessed by electron beam tomography has been shown to correlate well with the histomorphometric calcium area [22] and with the histopathologically established coronary atherosclerotic plaque area [23]. The total coronary calcium score, assessed by electron beam tomography, is strongly related to angiographically established coronary artery disease [24]. Second, the calcium score as constructed by Agatson *et al*. [16] uses both the area of calcification and the density, as a weighing factor of the calcified area. The density of a calcified lesion is coded as 1 to 4 depending on the maximum density in the area. This can result in an inaccurate score as only the maximum density is used as a weighing factor. The reproducibility of calcium scoring using the formula of Agatson *et al*. [16] has been shown to be limited [21,25]. At this moment, however, the calcium score based on the formula of

Fig. 1



Mean values of log coronary calcium across quartiles of aortic pulse wave velocity (PWV). Model adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes mellitus, antihypertensive medication, the use of statins, previous cardiovascular disease and carotid intima–media thickness.

Table 4 Linear regression coefficients describing the increase in log total calcium score per 1 m/s increase in pulse wave velocity in different categories of subjects

	β Coefficient and 95% CI
< 70 years	0.10 (0.00, 0.10)
≥ 70 years	0.09 (0.03, 0.16)
Men	0.05 (0.00, 0.10)
Women	0.09 (0.34, 0.16)
No diabetes mellitus	0.05 (0.01, 0.10)
Diabetes mellitus	0.17 (0.04, 0.31)
Non-smokers	0.06 (0.01, 0.11)
Smokers	0.01 (−0.09, 0.13)
Normotensive	0.07 (0.00, 0.14)
Hypertensive	0.52 (0.15, 0.89)
No previous CVD	0.06 (0.01, 0.10)
Previous CVD	0.12 (0.03, 0.20)

CI, Confidence interval; CVD, cardiovascular disease. Model adjusted for age, sex, mean arterial blood pressure, heart rate, body mass index, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes mellitus, antihypertensive medication, the use of statins, previous CVD and carotid intima–media thickness.

Agatson *et al*. [16] is the only widely accepted and available scoring system. Any misclassification of the total calcium score induced by using the formula of Agatson *et al*. [16] is likely to be independent of the aortic stiffness, and will therefore have led to an underestimation of the association.

We found a strong association between aortic stiffness and atherosclerosis of the coronary arteries, which is in accordance with some previous relatively small studies that showed increased aortic stiffness in high-risk patients with coronary artery disease assessed by angiography [12,13,26–28]. On the contrary, one previous study examined the association of aortic stiffness and coronary calcification measured by electron beam tomography in 190 asymptomatic men at risk of cardiovascular disease [11], but found no association. The relatively small number of subjects in the study, resulting in little power to disclose an association, might explain the discrepancy with our results. A recent study [29], performed in 401 adults without a history of myocardial infarction and stroke, found that aortic stiffness was strongly associated with coronary atherosclerosis, suggesting that aortic stiffness might be a biomarker of cardiovascular risk in asymptomatic individuals. The present study is a large population-based study showing an association between aortic stiffness and coronary atherosclerosis in a population of older individuals. The association also remained unchanged when we considered men and women separately, different age groups, and categories of subjects with and without diabetes mellitus, hypertension and a history of myocardial infraction and stroke.

Common determinants of arterial stiffness and atherosclerosis might partly explain the observed association. If this hypothesis is correct, an adjustment for common determinants of both processes is expected to attenuate the association between aortic stiffness and coronary

atherosclerosis. However, when an additional adjustment for the presence of cardiovascular risk factors as common determinants was performed, the strength of the association did not change. Besides common determinants, other mechanisms may explain the association between aortic stiffness and atherosclerosis of the coronary arteries. There is evidence that the presence of atherosclerosis leads to stiffening of the arteries [8]. Conversely, increased arterial stiffness may lead to atherosclerosis by vessel wall damage. Without its shock-absorbing capacity, the stiff arterial wall may be subjected to greater shear and intraluminal stresses as a result of increased pulsatile pressure [30]. Both atherosclerosis and arterial stiffness are likely to be generalized processes, occurring throughout the arterial system when present. If this is true, and if one process is a causal factor in the pathogenesis of the other and vice versa, one would expect to find a strong, synergistic, association between arterial stiffness and atherosclerosis independent of the vessel beds studied. Additional adjustment for the presence of atherosclerosis at other sites of the arterial tree attenuated the observed association, which is consistent with this view.

Increased aortic stiffness can lead to an increase in SBP, thereby increasing the workload and oxygen consumption of the heart, and simultaneously a decrease in DBP, thereby possibly limiting coronary perfusion [1]. A heart with a normal coronary circulation is capable of regulating coronary blood flow by means of vasodilatation to secure the metabolic needs of the myocardium even when the diastolic perfusion pressure declines [3]. In the presence of coronary artery disease, however, this regulation mechanism can be exhausted [4–7]. In these circumstances, a decline in aortic DBP and a subsequent decrease in coronary perfusion pressure can lead to myocardial ischaemia, especially subendocardial ischaemia. An experimental study in dogs showed that decreased aortic compliance greatly increased the risk of subendocardial ischaemia in the presence of coronary stenosis [31]. In a recent study [10], we were able to show that aortic stiffness predicts cardiovascular events in apparently healthy older adults. The present study, shows that subjects with increased aortic stiffness have advanced calcifications of the coronary arteries. This may indicate a group at risk of subendocardial ischaemia and subsequent cardiac events when the mechanism observed in animals also applies to humans. Antihypertensive therapy in individuals with isolated systolic hypertension and increased pulse pressure as a result of increased arterial stiffness may be hazardous because of lowering DBP. However, large clinical trials have shown that blood pressure-lowering drugs in subjects with isolated systolic hypertension and a high pulse pressure greatly decreased cardiovascular risk [32–34]. A recent meta-analysis that showed a large benefit of treating isolated systolic hypertension in the elderly, however, also showed that for every level of SBP, DBP was inversely associated with cardiovascular mortality [35]. This paradox might be explained by a greater favourable effect of antihypertensive therapy on cardiac oxygen demand by lowering SBP compared with the hazardous effect of antihypertensive therapy on cardiac oxygen supply by lowering DBP. Furthermore, several blood pressure-lowering drugs may also decrease stiffness of the arteries [36–40], which by itself may lead to an increase in DBP. Our results suggest that the effect of low DBP may be enhanced in individuals with increased arterial stiffness because of the concomitant presence of coronary atherosclerosis. Selectively lowering SBP without altering DBP may be indicated in individuals with a high pulse pressure caused by arterial stiffness [35,41].

In conclusion, the results of this population-based study in elderly subjects show that aortic stiffness is strongly related to atherosclerosis of the coronary arteries. Our findings suggest that measures of aortic stiffness might be a useful non-invasive surrogate marker for the extent of coronary atherosclerosis. As individuals with coronary atherosclerosis may have lost their ability to compensate for a decreased coronary perfusion resulting from increased aortic stiffness, it is important to recognize the frequent simultaneous concurrence of these conditions.

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