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RESEARCH LETTER

The association of arterial stiffness and arterial calcification: the Rotterdam Study

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The purpose of the present study was to examine the association between arterial stiffness and arterial calcification, in a population-based study, in subjects aged 55 years and above. Carotid-femoral pulse wave velocity (PWV) and cross-sectional distensibility coefficient (CSDC) were measured using ultrasound, and the values were categorized in quartiles. Aortic arch and carotid calcification was assessed by multislice computed tomography (MSCT) and quantified according to the Agatston score. Multivariate logistic regression was used and showed an independent association of aortic stiffness with carotid calcification. CSDC was independently associated with both aortic arch and carotid calcification.

Arterial stiffness has been found to be associated with atherosclerosis and has been shown to predict cardiovascular events.[1] However, data on the association between arterial stiffness and calcified atherosclerosis are limited.[2] More advanced atherosclerotic lesions contain calcification, although calcification may also be present in small amounts in the earlier stages of atherosclerosis. This study is embedded in the Rotterdam Study, a population-based study. The design and rationale of the Rotterdam Study have been described elsewhere.[3] During the third examination, between 1997 and 1999, measurements of cardiovascular risk factors and arterial stiffness were conducted. The fourth examination took place from 2002 to 2004. From September 2003 onwards, all participants who completed the fourth examination phase were invited to undergo an MSCT scan of the aortic arch and the carotid arteries. The present analyses were restricted to the participants who were scanned until December 2004. In 698 subjects, data of carotid calcification and at least one measurement of arterial stiffness were available. The aortic arch could not be evaluated in one subject, and hence data on calcification in the aortic arch were available for 697 subjects. The median duration between the third examination phase and the MSCT scan was 4.7 years. This study was approved by the Medical Ethics Committee and the Radiation Protection Unit of the Erasmus Medical Center, Rotterdam, the Netherlands. All participants gave written informed consent. Aortic stiffness was assessed by measuring carotid-femoral PWV, assessed with an automatic device (Complior Artech Medicla, Paris, France)[4] Data on aortic stiffness were available for 667 subjects (96%). Carotid distensibility was assessed as described elsewhere.[5] Data on CSDC were available for 607 subjects (87%). With the use of a standardized protocol, imaging was performed with a 16- or 64-slice MSCT scanner (SOMATOM Sensation 16 or 64, Siemens, Forcheim, Germany) in all subjects. The scan reached from the aortic arch to the intracranial circulation (1 cm above the sella turcica). Two reviewers scored arterial calcification using a standardized protocol, blinded to the clinical data of the participants. Calcified lesions were scored by using dedicated software (syngo Calcium Scoring, Siemens, Forcheim, Germany). For each calcified lesion, the Agatston score was calculated.[6] For image data with an overlapping reconstruction increment, Agatston scores were normalized with the ratio of increment and slice width. The total score per vessel bed was calculated by adding up the scores of all lesions. Information on cardiovascular risk factors was collected during the third follow-up examination. The missing values of covariates were handled by single imputation using an expectation-maximization algorithm.[7] The associations were examined using logistic regression with aortic arch or carotid calcifications as dependent variables and aortic stiffness and CSDC as independent variables. The dependent and the independent variables were categorized. The first quartile of the value of arterial stiffness, indicating the lowest stiffness, was used as the reference category. Initially, the regression analysis was adjusted for age, gender, mean arterial pressure, heart rate and type of MSCT (model 1). In model 2, additional adjustments were made for body mass index, serum total cholesterol, HDL-cholesterol, smoking, diabetes mellitus, and lipid- and blood pressure-lowering medication. The table with the characteristics of the population is presented in Supplementary Information. Fifty percent of the study population was men. The mean age (± s.d.) of the study participants during the arterial stiffness measurement was 68.7 years (± 5.4). Overall, calcium scores were higher in men than in women, and therefore gender-specific quartiles were used. Table 1 shows the odds ratio (OR) for the association between arterial stiffness and arterial calcification. We found an independent association of aortic stiffness with carotid calcification (OR (95% confidence interval)) of 2.1 (1.1–3.9) and 2.7 (1.3–5.3) for subjects in the third and fourth quartiles,

Table 1 Relation between arterial stiffness and calcification[a] in the aortic arch and the carotid arteries

	Aortic arch calcification		*Carotid artery calcification*	
	Model 1 OR (95% CI)	*Model 2 OR (95% CI)*	*Model 1 OR (95% CI)*	*Model 2 OR (95% CI)*
Aortic stiffness				
1st quartile	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd quartile	1.2 (0.6–2.2)	1.2 (0.6–2.2)	1.4 (0.7–2.5)	1.4 (0.7–2.8)
3rd quartile	1.5 (0.8–2.7)	1.4 (0.7–2.7)	2.2 (1.2–4.0)[b]	2.1 (1.1–3.9)[b]
4th quartile	1.8 (0.9–3.3)	1.8 (0.9–3.5)	2.7 (1.4–5.0)[c]	2.7 (1.3–5.3)[c]
CSDC				
1st quartile	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd quartile	1.3 (0.6–2.5)	1.2 (0.6–2.4)	1.9 (1.0–3.5)	1.9 (0.9–3.4)
3rd quartile	2.2 (1.1–4.2)[b]	1.9 (1.0–4.0)	2.3 (1.2–4.3)[b]	2.3 (1.0–4.0)[b]
4th quartile	3.0 (1.5–6.2)[c]	2.5 (1.2–5.4)[b]	3.6 (1.7–7.1)[d]	3.2 (1.4–6.0)[c]

Abbreviations: OR, odds ratio; CI, confidence interval.
Model 1 adjusted for age, gender, type of MSCT, mean arterial pressure and heart rate. Model 2 additionally adjusted for body mass index, serum total cholesterol, HDL-cholesterol, smoking, diabetes mellitus and lipid- and blood pressure-lowering medication.
[a]Highest quartile of calcification versus the lower three quartiles.
[b]$0.01<P<0.05$.
[c]$0.001<P<0.01$.
[d]$P<0.001$.

respectively, compared to subjects in the first quartile. The association of aortic stiffness with aortic arch calcification was less consistent. CSDC was independently associated with both aortic arch and carotid calcification (aortic arch calcification 2.6 (1.2–5.4), fourth versus first quartile; carotid calcification, 2.0 (1.0–4.0), 2.9 (1.4–6.0), third and fourth versus first quartile). Our study shows that aortic stiffness and carotid distensibility are independently associated with carotid calcification and that CSDC is independently associated with aortic arch calcification. Other studies have found an association between arterial stiffness and atherosclerosis.[8–11] Several explanations for our findings are possible. The presence of atherosclerosis may lead to arterial stiffening. It is likely that calcified plaques affect stiffness more than noncalcified plaques. However, this cannot be concluded from our data, since we were not able to examine the relation of stiffness with noncalcified plaques. Stiffening of the arterial wall increases shear stress and may lead to vessel wall damage and atherosclerosis. Since our study was cross-sectional, our data provide no information on which of the two latter mechanisms is more likely. Some limitations of our study need to be discussed. First, for determining arterial stiffness, we used data from the third examination phase, which was 4.7 years prior to the MSCT scan; this might have led to misclassification in the severity of arterial stiffness at the time of measurement of arterial calcification. However, we expect the misclassification to be nondifferential with respect to arterial calcification, which therefore might have led, if anything, to an underestimation of the associations. Second, nonparticipation of diseased subjects may have resulted in a relatively healthy study population, with a more restricted range of calcium scores and values of arterial stiffness, which might have lead to an underestimation of the associations. Third, in computing the carotid distensibility coefficient, we used the brachial pulse pressure rather than the carotid pulse pressure. Information on comparisons between the carotid and the brachial pulse pressure indicates that the carotid pulse pressure is lower than the brachial pulse pressure, but the differences are relatively small. The advantages of our study include the large population in a population-based setting and the inclusion of two measures of arterial stiffness in different vessel beds.

In conclusion, aortic stiffness and carotid distensibility are independently associated with carotid calcification, carotid distensibility is independently associated with aortic arch calcification, whereas the relation between aortic stiffness and aortic arch calcification was less consistent. These results support the view that arterial stiffness and arterial calcification are concurrent processes.

What is known about this topic

- Arterial stiffness is an age-related process associated with cardiovascular risk factors.
- Arterial stiffness is associated with cardiovascular disease.

What this study adds

- The first large population-based study that shows an association between CSDC and both carotid and aortic arch calcification.
- The first large population-based study that shows an association between aortic stiffness and carotid calcification.
- Our results support the view that arterial stiffness and arterial calcification are concurrent processes.

AE Odink[1,2], FUS Mattace-Raso[1,3], A van der Lugt[2], A Hofman[1], MGM Hunink[1,2], MMB Breteler[1], GP Krestin[2] and JCM Witteman[1]
[1]*Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands;*
[2]*Department of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands and*
[3]*Section of Geriatric Medicine, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands*
E-mail: j.witteman@erasmusmc.nl

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Supplementary Information accompanies the paper on the Journal of Human Hypertension website (http://www.nature.com/jhh)