Arterial Stiffness Is Associated With Carotid Intraplaque Hemorrhage in the General Population

The Rotterdam Study

Mariana Selwaness, Quirijn van Den Bouwhuijsen, Francesco U.S. Mattace-Raso, Germaine C. Vervoort, Albert Hofman, Oscar H. Franco, Jacqueline C.M. Witteman, Aad van der Lugt, Meike W. Vernooij, Jolanda J. Wentzel

Objective—The relation between arterial stiffness and atherosclerosis, and specifically the influence of arterial stiffness on plaque composition, is largely unknown. In a population-based study, we investigated the association between arterial stiffness and the presence and composition of carotid atherosclerotic plaques.

Approach and Results—Arterial stiffness was measured in 6527 participants (67.0±8.6 years) using aortic pulse wave velocity (PWV). Presence of carotid atherosclerotic plaques was assessed with ultrasound. Subsequently, 1059 subjects with carotid plaques (>2.5 mm) underwent MRI to assess plaque composition (presence of intraplaque hemorrhage, lipid, and calcification). Generalized estimation equation analyses adjusted for age, sex, mean arterial pressure, heart rate, carotid wall thickening, pulse pressure, and traditional cardiovascular risk factors were used to study the association between PWV and the presence and composition of carotid atherosclerotic plaques. In multivariable analysis, higher PWV was independently related to higher prevalence of carotid atherosclerotic plaque on ultrasound (odds ratio for highest quartile of PWV compared with lowest quartile, 1.24 [95% confidence interval, 1.02–1.51]). Furthermore, higher PWV was associated with intraplaque hemorrhage (age- and sex-adjusted odds ratio per SD increase in PWV, 1.20 [1.04–1.38] and calcification, 1.18 [1.03–1.35]), but not with lipid. After adjustment for cardiovascular risk factors, PWV remained significantly associated with intraplaque hemorrhage (1.20 [1.01–1.43]). Additional adjustment for pulse pressure did not materially affect the effect estimate (1.19 [1.00–1.42]).

Conclusions—Higher PWV is associated with presence and composition of carotid atherosclerotic plaques, in particular with intraplaque hemorrhage. These findings provide further clues for understanding the development of vulnerable atherosclerotic plaque. (Arterioscler Thromb Vasc Biol. 2014;34:00-00.)

Key Words: atherosclerosis ■ carotid arteries ■ vascular stiffness

Although arterial stiffness and atherosclerosis share some common determinants, such as increasing age, sex, and hypertension, it is unknown whether a gradual stiffening of the arterial wall may accelerate development of vulnerable plaque components, such as IPH. In a previous study, we showed that a single, cross-sectional measurement of the pulsatile component of blood pressure was associated with IPH. Arterial stiffness is the principal cause of increasing systolic blood pressure and pulsatility of flow, and therefore, PWV may reflect the cumulative damage on the arterial wall. Several studies have investigated the relation between arterial stiffness and aortic or coronary calcifications. However, the relationship between arterial stiffness and carotid plaque components, either calcification or vulnerable plaque components, has received less attention. By examining the role of vascular wall properties in the context of atherosclerosis formation, we...
aim to gain more insight in the pathogenesis of the vulnerable plaque.

MRI has emerged as a noninvasive imaging modality that enables accurate identification of the main components of the atherosclerotic plaque.\textsuperscript{17,18} The objective of this study was to investigate the association between arterial stiffness, as assessed by PWV, and the presence and various components of carotid atherosclerotic plaque in a large population-based cohort, using both ultrasound and MRI assessment of plaques.

### Materials and Methods

Materials and Methods are available in the online-only Supplement.

### Results

Among the 6527 subjects (67.0±8.6 years) who underwent carotid ultrasonography, 2527 (39.6%) subjects had ≥1 carotid plaques of ≥2.5 mm. Table 1 shows population characteristics of participants with ultrasound carotid plaques compared with those without plaques. Comparison of both groups showed that subjects with atherosclerotic plaque had a higher prevalence of various cardiovascular risk factors, including lower high-density lipoprotein cholesterol, higher systolic blood pressure, lower diastolic blood pressure, higher prevalence of smoking, diabetes mellitus, hypertension, antihypertensive medication use, history of myocardial infarction, and stroke (P<0.001). Of all persons with carotid plaque on ultrasound, to date, for 1059 subjects carotid MRI scanning was available (Table 1). Although the MRI population was significantly younger, had lower body mass index, systolic and diastolic blood pressure, lower prevalence of diabetes mellitus, and hypertension compared with subjects with carotid plaque ≥2.5 mm on ultrasound, the differences of the absolute values were small.

Table 2 shows the association between PWV and presence of plaque on ultrasound. In all models, higher quartiles of PWV were significantly associated to presence of plaque, when compared with the lowest quartile of PWV. Associations attenuated when additionally adjusted for pulse pressure (model 3), but remained significant for the second, third, and fourth quartile of PWV compared with the first quartile, with respective odds ratios (ORs) (95% confidence interval) of 1.18 (1.01–1.37), 1.41 (1.19–1.66), and 1.27 (1.05–1.54). Subsequently, we investigated whether PWV was linearly related with the presence of plaque, but the linear trend for the association between PWV (per SD increase) and presence of plaques was not significant in the full model (OR, 1.06 [0.99–1.14]).

Table 3 describes the MRI plaque characteristics in 1979 carotid arteries with wall thickening on MRI. Median (interquartile range) of carotid wall thickness on MRI and degree of stenosis was 3.0 (2.6–3.6) mm and 4.3% (0%–20.6%), respectively. MRI revealed presence of IPH in 520 (26.3%), lipid in 552 (27.9%), and calcification in 1444 (73%) of carotid plaques.

Table 4 shows the association of PWV (per SD increase) with presence of the various MRI-defined plaque components. PWV was significantly associated with presence of IPH (age-, sex-, and interval-adjusted OR per SD increase in PWV, 1.20 [1.04–1.38]; model 1). Additional adjustments for mean arterial pressure, heart rate, antihypertensive medication, carotid wall thickness (model 2), and pulse pressure (model 3) only slightly attenuated this association. In the fully adjusted model (model 5), each SD increase in PWV increased the likelihood of IPH by ≥20% (OR, 1.19 [95% confidence interval, 1.00–1.42]; P=0.05). The OR for the association between PWV and lipid was 1.13 (0.97–1.31), but lacked statistical significance. The association between PWV and calcification was inconclusive; although in model 1 the association was significant (OR, 1.18 [95% confidence interval, 1.03–1.35]; P=0.02), in multivariable analyses the effect size decreased and was no longer significant (OR, 1.10 [95% confidence interval, 0.93–1.31]; P=0.2).

The analyses stratified for time interval between PWV and MRI showed no effect modification by time interval (Table 1 in the online-only Data Supplement). In both strata, the association between PWV and IPH was similar. Only for calcification, the effect estimate between PWV and presence of calcification was larger in the stratum with short time interval compared with long time interval (OR, 1.59 versus 1.10; P interaction=0.8; Table 1 in the online-only Data Supplement).

### Discussion

In this large, population-based cohort, we provide evidence that arterial stiffness is associated with presence and composition of carotid atherosclerotic plaques in the general population. By measuring aortic PWV, we found that arterial stiffness was independently associated with presence of plaques in the carotid arteries. Furthermore, among individuals with a plaque in the carotid arteries, arterial stiffness was an important determinant of IPH, independent of plaque size, pulse pressure, and other cardiovascular risk factors. Associations between arterial stiffness and lipid or calcification were less pronounced.

Our finding that PWV is associated with presence of carotid atherosclerosis is in agreement with the Atherosclerosis Risk in Communities (ARIC) Study. In >10000 subjects, reduced arterial elasticity was significantly associated with carotid intima–media thickness in the 90th percentile.\textsuperscript{19} Also, within the Rotterdam Study, it was previously shown that mean PWV was higher in subjects with moderate and severe carotid plaque score as compared with those without plaque.\textsuperscript{20} However, our study extended this previous study population with on average younger subjects of additional cohort extensions (RS-II and RS-III), and we restricted definition of carotid atherosclerosis to intima–media thickness of ≥2.5 mm. Carotid intimal thickening represents one of the earliest manifestations of subclinical atherosclerosis. It has been suggested that lower degrees of intima–media thickness, an adaptive response to local hemodynamic changes, may be reflected rather than atherosclerotic thickening, which is represented beyond a certain level.\textsuperscript{21} According to the Cardiovascular Health Study, 0.9 mm was considered as the threshold for the association with...
an increased risk of myocardial infarction and stroke in participants aged >65 years. Our definition of plaque (intima–media thickness ≥2.5 mm) might thus be regarded as a more advanced manifestation of atherosclerosis. This is supported by earlier works in which, in 564 healthy subjects, arterial stiffness independently correlated with carotid atherosclerotic plaques, but not with diffuse common carotid intimal thickening at the plaque-free sites.

In addition, we found arterial stiffness to be differently associated with different plaque components, suggesting involvement of vascular wall properties in the formation of the various plaque components. Studies investigating the relation between arterial stiffness and plaque composition are scarce. Moreover, ultrasonography, the most commonly used imaging modality for carotid plaque evaluation, is limited to a differentiation between echogenic and echolucent plaques. The use of MRI for the assessment of plaque composition has now been widely accepted, and MRI has the ability to reliably assess presence of IPH, lipid, and calcification. One study that investigated arterial stiffness, measured as carotid distensibility, and plaque composition as detected with MRI found no association between carotid distensibility and plaque composition. A difference between that study and ours is that local distensibility was measured instead of the global parameter PWV.

The most interesting finding of our present study is that arterial stiffness is associated with the presence of IPH in the general population. This is important because IPH is considered as a risk indicator for plaque instability. Several mechanisms may explain the association between arterial stiffness and plaque IPH.
Table 3. Plaque Characteristics on MRI (n=1979 Carotid Arteries)

<table>
<thead>
<tr>
<th>Plaque Characteristics on MRI (n=1979 Carotid Arteries)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid wall thickening on MRI, mm</td>
<td>3.0 (2.6–3.6)</td>
</tr>
<tr>
<td>Degree of stenosis, %</td>
<td>4.3 (0–20.6)</td>
</tr>
<tr>
<td>Presence of IPH</td>
<td>520 (26.3)</td>
</tr>
<tr>
<td>Presence of lipid</td>
<td>552 (27.9)</td>
</tr>
<tr>
<td>Presence of calcification</td>
<td>1444 (73.0)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) for continuous variables and percentages for dichotomous variables. IPH indicates intraplaque hemorrhage.

Table 4. Association Between PWV (per Increase in SD) and Various Plaque Components (n=1979 Carotid Plaques)

<table>
<thead>
<tr>
<th>Model</th>
<th>Intraplaque Hemorrhage</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Lipid</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Calcification</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.20 (1.04–1.38)</td>
<td>0.01</td>
<td>1.06 (0.92–1.21)</td>
<td>0.4</td>
<td>1.18 (1.03–1.35)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1.22 (1.03–1.45)</td>
<td>0.03</td>
<td>1.10 (0.95–1.28)</td>
<td>0.2</td>
<td>1.14 (0.97–1.35)</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1.21 (1.01–1.44)</td>
<td>0.03</td>
<td>1.12 (0.96–1.30)</td>
<td>0.2</td>
<td>1.12 (0.95–1.32)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>1.20 (1.01–1.43)</td>
<td>0.04</td>
<td>1.11 (0.96–1.29)</td>
<td>0.2</td>
<td>1.13 (0.95–1.33)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 5</td>
<td>1.19 (1.00–1.42)</td>
<td>0.05</td>
<td>1.13 (0.97–1.31)</td>
<td>0.1</td>
<td>1.10 (0.93–1.31)</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, and time interval between PWV and MRI measurement. Model 2: adjusted as in model 1+mean arterial pressure, heart rate, antihypertensive medication, and carotid wall thickness. Model 3: adjusted as in model 2+pulse pressure. Model 4: adjusted as in model 2+body mass index, total cholesterol, HDL cholesterol, smoking, diabetes mellitus, history of myocardial infarction or stroke. Model 5: adjusted as in model 3+body mass index, total cholesterol, HDL cholesterol, smoking, diabetes mellitus, history of myocardial infarction or stroke. CI indicates confidence interval; HDL, high-density lipoprotein; OR, odds ratio; and PWV, pulse wave velocity.
susceptible to calcification and thus leads to less distensibility. Nevertheless, we did not find a pronounced association between arterial stiffness and plaque calcification, although this would have been expected from the biomechanical perspective that calcification leads to vessel stiffening. One explanation may be that PWV reflects global arterial stiffness and not necessarily vessel stiffness on the calcified site. Also, it is known that carotid calcification load only moderately correlates with aortic calcification. Previous studies found inconsistent associations between arterial stiffness and plaque calcification. A previous cross-sectional study within the Rotterdam Study found an independent association of arterial stiffness, measured as carotid–femoral PWV and carotid distensibility coefficient, with carotid calcification. In contrast to our study, calcification was measured using computed tomography and quantified according to the Agatston score. Whereas with MRI, we can only distinguish between presence and absence of calcification, with computed tomography and the Agatston score, more detailed and quantitative information is captured about the amount of calcification. Furthermore, PWV was measured on average 4.7 years before computed tomography, but ≤10.9 years before the MRI scanning. Although we found no significant effect modification of the time interval between PWV measurement and MRI, the lack of a pronounced association between PWV and calcification in the present study may have been influenced by the relatively long interval in part of our population, because the association with calcification tended to be weaker with increasing distance between measurements.

This study is limited by several methodological aspects which need to be discussed. First, identification of plaque characteristics within small plaques (<2 mm) was not feasible because of constraints in spatial resolution of MRI. This may have resulted in an under-reporting of the prevalence of the different plaque components. Second, we cannot completely exclude a possible link between arterial stiffness and lipid plaques because application of contrast-enhanced MRI, which improves identification of lipid, was not possible in this population-based setting. Third, we did not measure arterial stiffness and plaque calcification on the same location, which may have reduced the association of arterial stiffness with this plaque component.

In conclusion, our study shows that PWV is associated with presence of atherosclerotic plaques and with plaque composition, in particular IPH. These findings provide further clues for understanding the development of vulnerable atherosclerotic plaque.

Sources of Funding
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Disclosures
None.

References

Significance

Carotid atherosclerotic plaque composition, and in particular the presence of intraplaque hemorrhage, has been shown to be related to plaque instability, which is thought to increase the risk of cerebral ischemia. We hypothesized a link between arterial stiffness and atherosclerotic plaque composition. In a general population, we investigated the association of arterial stiffness, as assessed by pulse wave velocity, with presence and composition of carotid atherosclerotic plaques. MRI was used to assess plaque composition. Pulse wave velocity was found to be associated with presence of carotid atherosclerotic plaques and appeared to be an independent determinant of intraplaque hemorrhage. The current findings suggest that arterial stiffness affects atherosclerotic plaque characteristics and provide further clues for understanding atherosclerotic plaque formation in the carotid arteries.
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MATERIALS AND METHODS

Study population
The Rotterdam Study I (RS-I) is a prospective population-based cohort study among 7,983 participants aged ≥55 years which started in 1990-1993 and aimed at investigating determinants of various chronic diseases. In 2000-2001, the Rotterdam Study was expanded (RS-II) with 3,011 participants who had become ≥55 years of age or had moved into the study district. In 2006, a further extension of the cohort was initiated (RS-III) in which 3,932 subjects were included, aged ≥45 years, fulfilling the same inclusion criteria as the original cohort. All participants are invited every three to four years to the research center for follow-up examinations, including carotid ultrasonography. Arterial stiffness measurements by means of PWV were conducted in 1997-2001 (RS-I and RS-II) and in 2006-2007 (RS-III). Since 2007, carotid MRI scanning has been performed in the Rotterdam Study. All participants with carotid wall thickening on a previous ultrasound examination were invited for carotid MRI scanning. The Medical Ethics Committee of Erasmus Medical Center approved the study protocol and written informed consent was obtained from all participants. The study procedures were in accordance with institutional guidelines.

Pulse wave velocity
Aortic PWV was measured with subjects in supine position. Measurements of PWV were performed during the morning or afternoon (no specific time) and the subjects were non-fasting. The PWV was assessed with an automatic device (Compilor Artech Medical, Pantin, France) that measures 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 between the recording sites in the carotid and the femoral artery was measured with a measurement tape over the surface of the body. The PWV was calculated as the ratio between distance and the foot-to-foot time delay, and was expressed in meters per second. Mean arterial pressure (MAP) and heart rate (HR) were recorded simultaneously as described previously.

Ultrasound measurements
Ultrasonography of the common carotid artery, carotid bifurcation and internal carotid artery of the left and right carotid arteries was performed using a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV). The ultrasonography protocol and reading has been described in detail previously. For each individual, carotid wall thickening was determined as the maximum near and far wall measurements. Carotid wall thickening was reported as present if intima-media wall thickness (IMT) ≥2.5mm was observed in at least one of the carotid arteries.

Magnetic resonance imaging
Carotid MRI scanning was performed on a 1.5 Tesla scanner with a bilateral phased-array surface coil. Two-dimensional (2D) time-of-flight MR angiography was performed to cover the carotid bifurcation at both sides ranging from 15 mm caudal to 30 mm cranial from the point of bifurcation. High-resolution images were obtained using a 30 minutes standardized protocol that included four 2D axial sequences, (a) PDw Fast Spin Echo (FSE) Black-blood (BB) sequence with fat suppression; (b) PDw-FSE-BB sequence with an increased in-plane resolution; (c) a PDw-EPI sequence; (d) T2w-EPI sequence, and two 3D sequences (I) 3D-T1w-GRE sequence parallel to the common carotid artery, and (II) 3D phased-contrast MR-Angiography. Sequence parameters have been described in detail elsewhere. The quality of all MRI sequences was rated on a five-point scale (1=worst; 5=best). Scans were included in the analyses if the image quality was scored ≥3 on all MRI sequences. All carotid arteries were reviewed for presence of atherosclerotic plaques (≥2.0 mm on MRI) and we
subsequently assessed each plaque for the presence of IPH, calcification and lipid as previously described.\textsuperscript{4}

Covariates
Information on covariates was collected through home interviews or was measured at the study center visit as described previously.\textsuperscript{5} Based on weight and height, the body mass index (BMI) was calculated. Blood pressure was measured using a random-zero sphygmomanometer at the study center visit and pulse pressure was calculated as the difference between the systolic and diastolic blood pressure. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol values were measured using standard laboratory techniques. Smoking status was classified as current, past and never. Diabetes mellitus was considered to be present when fasting blood glucose exceeded 7.0 mmol/L, when non-fasting glucose exceeded 11.0 mmol/L, or when antidiabetic medication was used. Hypertension was defined as the use of antihypertensive medication or a blood pressure of 140/90 mmHg or above.\textsuperscript{7} Antihypertensive drugs included diuretics, beta blockers, calcium blockers and ACE inhibitors. History of myocardial infarction or stroke was assessed until date of inclusion as previously described.\textsuperscript{8}

Population for analysis
PWV measurements were available in 6,915 of the Rotterdam Study participants, which is 60\% of the eligible subjects (n=11,740) in this cohort. Missing information on PWV measurements was almost entirely due to logistic reasons, in particular malfunctioning equipment or unavailability of technicians. Among persons with PWV measurements, ultrasonography of the carotid arteries was available for 6,527 subjects (94\%). Of these, 2,517 subjects had an atherosclerotic plaque ≥2·5mm in at least one of the carotid arteries. At the time of the present study, of these subjects, 1,439 had been invited for MRI of the carotid arteries. Of these, 380 subjects were not scanned because of claustrophobia, contraindications for MRI, refused to participate, or were excluded because of a scan with insufficient image quality. In the 1,059 subjects with an interpretable MRI scan, 1,979 carotid arteries had an atherosclerotic plaque (>2.0 mm on MRI) and were used for further analyses.

Statistical analysis
Data are expressed as mean±standard deviation (SD) for quantitative variables and percentages for discrete variables. We used logistic regression models to assess the association between PWV and carotid wall thickening on ultrasound. PWV was analyzed both in quartiles of its distribution (categorical) and per SD increase (continuous) in these models. For the analyses with PWV in quartiles of its distribution, the first quartile, indicating the lowest arterial stiffness, was used as the reference category. The model was first adjusted for age and sex (model 1) and additionally for MAP, HR, antihypertensive medication (model 2), pulse pressure (model 3) and cardiovascular risk factors (BMI, total cholesterol, HDL, smoking, diabetes and prevalent cardiovascular diseases (model 4).

To study the association of PWV with different atherosclerotic plaque components on MRI, ORs were estimated per SD increase in PWV. To adjust for the correlation between plaques in the two carotid arteries of the same participant, we performed Generalized Estimation Equation (GEE) with an unstructured working correlation matrix including two levels per participant, namely the left and right carotid artery. All analyses were initially adjusted for age at PWV measurement, sex, time interval between PWV and MRI scan (model 1), MAP, HR, antihypertensive mediation and carotid wall thickness (model 2), and subsequently also for pulse pressure (model 3). In models 4 and 5, we additionally added cardiovascular risk factors to the models without pulse pressure (model 2) and with pulse pressure (model 3), respectively.

Because of the population composition, participants with PWV measurements conducted in 1997-2001 (RS-I and RS-II) had a longer time interval between PWV measurement and MRI compared to persons with PWV measurements in 2006-2007 (RS-III) (mean interval 10.9±0.2 years and 0.8±2.3 years, respectively). To study the effect of this
time interval, we additionally analyzed the association between PWV and plaque composition stratified for time interval and tested for effect modification. All analyses were carried out using SPSS Statistical Package version 20.0 (Chicago, IL, USA). Missing values in the covariates were imputed using the Expectation Maximization method.  

References

**Supplementary table I.** Association between pulse wave velocity and different plaque components stratified for time interval between both measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of carotid plaques</th>
<th>Median (IQR) time interval (years)</th>
<th>Intraplaque haemorrhage OR, (95%CI), P-value</th>
<th>Lipid OR, (95%CI), P-value</th>
<th>Calcification OR, (95%CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short interval</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>313</td>
<td>0.8 (0.2)</td>
<td>1.18 (0.97-1.95) 0.5</td>
<td>0.91 (0.55-1.48) 0.7</td>
<td>1.59 (0.92-2.78) 0.1</td>
<td></td>
</tr>
<tr>
<td><strong>Long interval</strong></td>
<td>1,666</td>
<td>10.9 (2.3)</td>
<td>1.21 (1.01-1.45) 0.04</td>
<td>1.08 (0.92-1.27) 0.3</td>
<td>1.10 (0.93-1.30) 0.2</td>
</tr>
<tr>
<td><strong>p-value for interaction</strong></td>
<td></td>
<td>0.7</td>
<td>0.5</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

Interval presented as median (interquartile range) in years. Model adjusted for age, sex, time interval between PWV and MRI, MAP, HR and carotid wall thickness. OR=Odds ratio