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Hypertension. published online January 21, 2013;

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Multimodality Imaging of Subclinical Aortic Atherosclerosis

Relation of Aortic Stiffness to Calcification and Plaque in Female Twins

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Abstract—Aortic stiffness, an important predictor of cardiovascular events, may relate to aortic calcification rather than noncalcified atherosclerotic plaque. The aim of this study was to determine the relation of aortic stiffness to aortic plaque and aortic calcification in asymptomatic postmenopausal women. One hundred female twins (mean age±standard deviation 64±7 years) underwent computed tomography and magnetic resonance imaging (black-blood sequence) of the aorta. The topographical relation of plaque on magnetic resonance images and calcification on computed tomography images was assessed on magnetic resonance/computed tomography fused images. Carotid–femoral pulse wave velocity was used as a measure of aortic stiffness. Aortic plaque was identified in 87% and calcification in 65% of subjects, both increased with age and were higher in the abdominal compared with thoracic aorta ($P<0.0001$). Plaque correlated with calcification ($R=0.68$; $P<0.0001$), but was also detected in 58% of women who had no calcification. Pulse wave velocity (adjusted for age and blood pressure) increased across quartiles of calcification ($P<0.01$) but not plaque score ($P=0.56$). Shared genetic factors accounted for >99% of the correlation (0.35) between PWV and calcification. In conclusion, there is a high prevalence of subclinical atherosclerosis within the aorta in asymptomatic middle-aged women. Aortic stiffening relates to aortic calcification, but not to atherosclerotic plaque burden, and the association of aortic stiffness with calcification is driven by common genes. (*Hypertension*. 2013;61:XXX-XXX.)

Key Words: arteriosclerosis ■ atherosclerosis ■ genetics ■ imaging ■ twins

Aortic stiffening, as measured by aortic pulse wave velocity (PWV), is a major risk factor for cardiovascular events^{1–3} and has been attributed to atherosclerosis within the aorta.^{4,5} Because aortic atherosclerosis is an invariable accompaniment of clinical or subclinical manifestations of atherosclerosis within the coronaries and other branches of the aorta,^{6,7} such a relation between aortic stiffening and aortic atherosclerosis would potentially explain the prognostic impact of aortic stiffening in terms of it being a marker for atherosclerosis. However, in primate models of atherosclerosis, development of atherosclerotic plaque in the aorta is not necessarily associated with aortic stiffening.⁸ Conversely, induction of medial calcification in animal models leads to stiffening of large elastic arteries in the absence of intimal plaque formation.⁹ In humans, aortic stiffening is associated with calcification, but whether this is a result of coexisting atherosclerotic plaque is unknown; inference from the carotid artery suggests that it may be independent of noncalcified atheromatous plaque.¹⁰ The purpose of the present study was to examine the relationship between

aortic PWV and characteristics of subclinical aortic wall disease in postmenopausal female twins. We used combined computed tomography (CT) and magnetic resonance imaging (MRI) to characterize calcified and noncalcified aortic plaque and to identify aortic calcification in the absence of plaque. We performed a heritability analysis to examine whether the relationship between aortic stiffness and wall characteristics might be explained by shared genes.

Methods

Subjects

Subjects were 100 asymptomatic postmenopausal female twins (21 monozygotic [MZ] and 24 dizygotic [DZ] pairs) recruited from the Twins UK cohort,¹¹ with similar characteristics to the general U.K. population.¹² All subjects underwent measurement of biochemical risk factors, aortic PWV, and thoracic–abdominal MR and CT imaging to quantify aortic plaque and calcium volume. The study was approved by St. Thomas' Hospital Research Ethics Committee, and written informed consent was obtained from all subjects.

Received August 14, 2012; first decision November 28, 2012; revision accepted December 12, 2012.

From the King's College London British Heart Foundation Centre, Department of Clinical Pharmacology, St. Thomas' Hospital, London, UK (M.C., P.C.); Division of Imaging Sciences and Biomedical Engineering, King's College London, St. Thomas' Hospital, London, UK (T.H., G.G., R.B.); Department of Radiology, Guy's and St. Thomas' Hospital, London, UK (R.P.); and King's College London, Department of Twin Research and Genetic Epidemiology, St. Thomas' Hospital, London, UK (A.M., T.D.S.).

Correspondence to P.J. Chowienzyk, Department of Clinical Pharmacology, St. Thomas' Hospital, Lambeth Palace Rd, London SE1 7EH, United Kingdom. E-mail phil.chowienzyk@kcl.ac.uk

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Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.111.00024

Biochemistry

Fasting serum total-cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), triglycerides, creatinine, calcium, phosphate, vitamin D (25-hydroxyvitamin D), and parathyroid hormone (PTH) were measured in all participants. Low-density lipoprotein cholesterol (LDL-cholesterol) was estimated using the Friedewald equation.

Cardiovascular MRI and CT

MR imaging was performed using a 1.5-T Achieva MR scanner (Philips Healthcare, Best, The Netherlands) and 5-element cardiac phased-array receiver coil, as previously described.¹³ Briefly, the aorta was visualized by obtaining 66 transverse slices (no slice gaps) spanning from the aortic arch to the aortic bifurcation (2 slabs of 33 slices centred about the thoracic and abdominal aorta, respectively) using a small field-of-view (zoom imaging) free-breathing electrocardiogram-triggered, double inversion, black-blood, 2-dimensional proton density weighted, turbo-spin-echo sequence.¹³ To maximize signal-to-noise, the cardiac coil was centered about the thoracic and abdominal aorta, respectively. Other imaging parameters included the following: pixel bandwidth 416 Hz, repetition time of 2 heart beats, shortest trigger delay (≈ 500 ms), inversion time ≈ 500 ms, echo time of 5.0 ms, 60 ms acquisition window, 12 lines per heart beat, field of view 220×67 , acquired matrix size 224×208 (acquired resolution 0.98×1.06 mm), slice thickness 5 mm, and partial Fourier imaging factor 0.75. Thoracic imaging was respiratory-gated using an 8-mm navigator window, and compensation for respiratory motion in the abdominal aorta was achieved using 2 signal averages. Noncontrast-enhanced CT was performed with a 64-slice CT helical scanner (Brilliance, Philips Medical Systems, Cleveland, OH). Transverse slices (5 mm) were acquired between the aortic arch and the aortic bifurcation.¹⁴ Although this is a relatively high slice thickness, this makes little difference to the total calcium score as calculated below, which is integrated over all slices.

Aortic Plaque and Calcium Analysis

MR and CT images were viewed offline simultaneously using OsiriX Medical Imaging Software (Geneva, Switzerland; www.osirix-viewer.com). Atherosclerotic plaque was determined from MR images and calcification from CT images. MR/CT images were coregistered using the aortic arch and aortic bifurcation to register thoracic and abdominal images, respectively. This method of CT/MRI coregistration has previously been shown to give precise comparison of calcified plaque lesions¹⁵ and to localize inflammation within lipid-rich plaque areas.¹⁶ Slices with poor image quality were excluded from the analysis. For each coregistered cross-sectional image slice, a region of interest was drawn around the aortic lumen and area was recorded.

On MR images, plaque was defined as a luminal protrusion relative to adjacent structures >1 mm in radial thickness for the entire wall.¹⁷ For each plaque, maximal radial thickness and plaque area was determined using a semiautomatic interactive tool. On CT images, calcium was defined as any area >1 mm² with attenuation ≥ 130 Hounsfield units and calcium area was recorded for each image slice.

The topographic relation of plaque and calcification was classified into the following: noncalcified plaque, where plaque was present independently of any evidence of calcification on fused images; calcified plaque, where plaque and calcification were colocalized; and calcification and no plaque, where calcification was present without any evidence of plaque on the MR image. Prevalence of plaque and calcification was defined in terms of the number of cross-sectional images in which they were present. Intraluminal plaque score and calcification score were estimated using plaque and calcium cross-sectional areas calculated as percentage of total vessel cross-sectional area: $(\sum \text{plaque/calcium cross-sectional area} / \sum \text{aortic cross-sectional area}) \times 100\%$.

Pulse Wave Velocity

Aortic PWV was determined noninvasively using the SphygmoCor system (AtCor, Australia) by sequentially recording the pressure pulse in the carotid and femoral artery, referenced to the R-wave of the electrocardiogram.¹⁸ Difference in pulse arrival was taken as transit time, and path distance was estimated as the distance between the

sternal notch and femoral artery. PWV was calculated by dividing distance by transit time. Measurements were made in triplicate and mean values used for analysis.

Statistical Analysis

The sample size was selected to give $>80\%$ power to detect a correlation of age-adjusted variables accounting for $>10\%$ of the variance in PWV at $P < 0.05$. Data analysis was performed using SPSS software (version 16.0, SPSS, Inc, Chicago, IL). Subject characteristics are presented as mean \pm SD unless otherwise stated. Significantly skewed variables were logarithmically transformed. Comparisons between groups were made using Student *t* test, χ^2 test, and ANOVA. Association between plaque and calcium burden was examined using Spearman rank correlation coefficient. Associations between PWV, demographic, and biochemical measures were examined using Pearson correlation coefficient. Multivariable regression analysis was then performed to examine independent predictors of PWV. Calcium and plaque scores were included in the model together with variables significantly correlated with PWV on univariate analysis or variables known to be associated with PWV from previous studies.

Heritability Analysis

Univariate and bivariate heritability analysis of plaque and calcium burden was performed using the classic twin model.¹⁶ Briefly, for univariate analysis, a greater similarity between genetically identical MZ twin pairs compared with DZ twins, that share on average 50% of their genes, suggests a genetic influence. The intraclass correlation coefficient was estimated for MZ and DZ twins to examine twin resemblance. For heritability estimates, the observed phenotypic variance was assumed to derive from additive genetic (a^2), common environmental (c^2), and unique environmental (e^2 , incorporating measurement error) components (ACE model). The common environmental component (c^2) estimates the contribution of family environment, which is assumed to be equal in both MZ and DZ twin pairs, whereas the unique environmental component (e^2) estimates the effects that apply only to each individual, including measurement error. Any greater similarity between MZ twins than DZ twins is attributed to a genetic influence. Structural equation modeling was used to estimate parameters of the ACE model and corresponding confidence intervals using the method of maximum likelihood (Mx software, University of Virginia). Significance of each parameter was determined by likelihood ratio tests. The contribution of shared genetic and environmental factors to the correlation between PWV and calcium score was investigated using bivariate analysis.¹⁹ A common genetic basis of this correlation was explored by examining cross-trait, cross-twin correlations, where a higher correlation between MZ in comparison with DZ twin pairs indicates a shared genetic influence. The phenotypic correlation between PWV and calcification was partitioned into that explained by additive genetic factors, shared environment, and nonshared environment.¹⁰

Results

Characteristics of MZ and DZ twins were similar and are listed in Table 1. Average age was 64 years (range 51–80 years). The average number of aortic images analyzed was 46.3 per subject. Of these, 3.3 (7.1%) images per person were excluded from analysis because of poor image quality. The intraobserver coefficients of variation of aortic plaque and calcium scores obtained from repeat analysis of 10 consecutive subjects were 1.27% and 0.63%, respectively.

Prevalence of Plaque and Calcification

Figure 1 illustrates typical images showing noncalcified plaque, calcified plaque, and calcification with no plaque. Aortic plaque was identified in 87% of subjects and calcification in 65% of subjects. Considering all cross-sectional images, 34% demonstrated plaque and in 14% plaque colocalized with

Table 1. Characteristics of Monozygotic (MZ) and Dizygotic Twins (DZ)

Characteristic	MZ Twins n=46	DZ Twins n=54
Age, y	65.2±6.9	64.3±7.6
Height, cm	160.2±5.9	162.2±5.4
Weight, kg	65.7±10.8	65.5±8.9
Systolic blood pressure, mm Hg	130.2±17.4	128.5±16.9
Diastolic blood pressure, mm Hg	73.8±8.9	75.2±10.9
Mean arterial pressure, mm Hg	95.6±10.7	94.8±12.2
Total cholesterol, mmol/L	5.85±1.37	5.75±0.97
HDL-cholesterol, mmol/L	2.19±0.55	2.07±0.48
LDL-cholesterol, mmol/L	3.13±1.24	3.25±0.82
Antihypertensive therapy, n	14	13
Lipid-lowering therapy, n	14	13
Diabetes mellitus, n	1	0
Current smoker, n	12	9
Former smoker, n	2	4

HDL-cholesterol indicates high-density lipoprotein cholesterol; and LDL-cholesterol, low-density lipoprotein cholesterol.

Values are means±SD.

calcification; 1.5% of cross-sectional images had calcification but showed no evidence of plaque on MR. Average plaque and calcification scores were 2.5% and 1.0%, respectively. Prevalence of plaque and calcification, according to the number of cross-sectional images, increased with age (each $P<0.001$) and were significantly higher in the abdominal aorta compared with the thoracic aorta (each $P<0.0001$). The correlation between plaque and calcification score was 0.68 ($P<0.0001$). In patients without aortic calcification, plaque was detected in 18 out of 31 (58%) participants, and plaque score ranged from

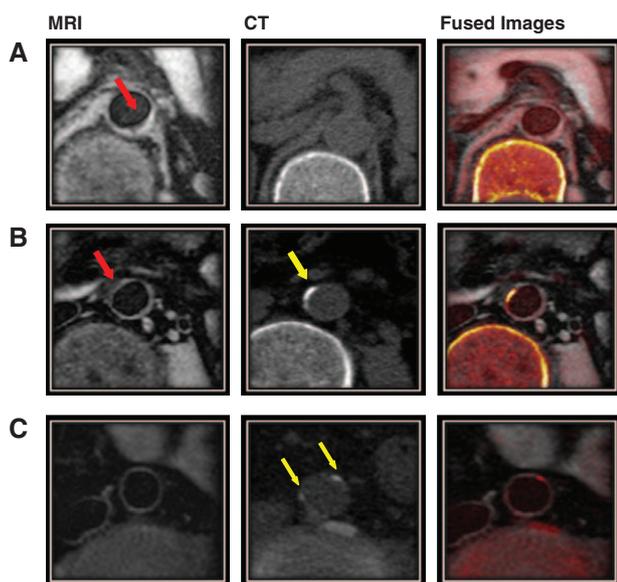


Figure 1. Example of computed tomography (CT), magnetic resonance imaging (MRI), and fused images for noncalcified plaque (A), calcified plaque (B), and calcification only (C). Red arrows indicate presence of plaque, and yellow arrows indicate presence of calcification.

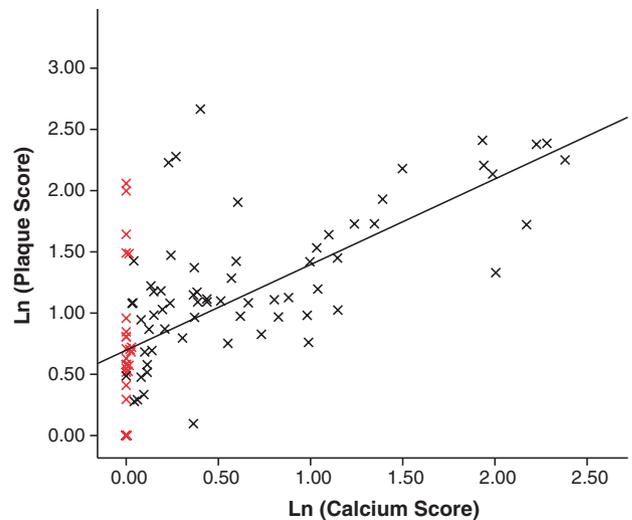


Figure 2. Correlation between plaque and calcium burden. Red crosses indicate range of plaque burden in individuals with low calcium burden.

0.32% to 6.84% (Figure 2). To determine the overlap between high plaque and calcium, women were categorized into quartiles according to plaque and calcium score. The proportion of women who were in each quartile of calcium score according to plaque score is shown in Figure 3A. All women with plaque scores in the first quartile of the distribution also had a low calcium score. When categorized according to calcium score (Figure 3B), women with calcium score in the first quartile had a variable amount of plaque, with 16% of these women having a plaque score in the third and fourth quartiles.

Relation of Arterial Stiffness to Aortic Plaque and Calcification

PWV was significantly correlated with age ($R=0.4$; $P<0.0001$), blood pressure ($R=0.35$; $P<0.0001$ for mean arterial pressure), and heart rate ($R=0.26$; $P<0.05$), but not with other demographic or biochemical risk factors. After adjustment for age, mean arterial pressure, and antihypertensive treatment, PWV increased across quartiles of calcium score but not plaque score ($P<0.01$ and $P=0.56$, respectively; Figure 4). In multivariable regression analysis, after adjustment for age, mean arterial pressure, and heart rate, PWV was significantly positively associated with calcium ($\beta=0.29$; $P<0.01$) but not plaque score (Table 2).

Heritability

Intraclass correlation coefficients for plaque and calcium score were greater for MZ compared with DZ twin pairs (Table 3), indicating a genetic influence on all phenotypic traits. The fully adjusted ACE model confirmed an additive genetic component accounting for 77% (95% confidence interval, 0.32–0.89) of the variance in calcium score. Estimated heritability for plaque score was lower at 41% (0.00–0.73) and not statistically significant. The within-twin correlation between PWV and calcium score was 0.35 ($P<0.01$). The cross-twin, cross-trait correlation was higher in MZ ($R=0.27$; $P=0.08$) compared with DZ ($R=0.23$; $P=0.11$) twins, suggesting that a shared genetic influence contributes to the observed

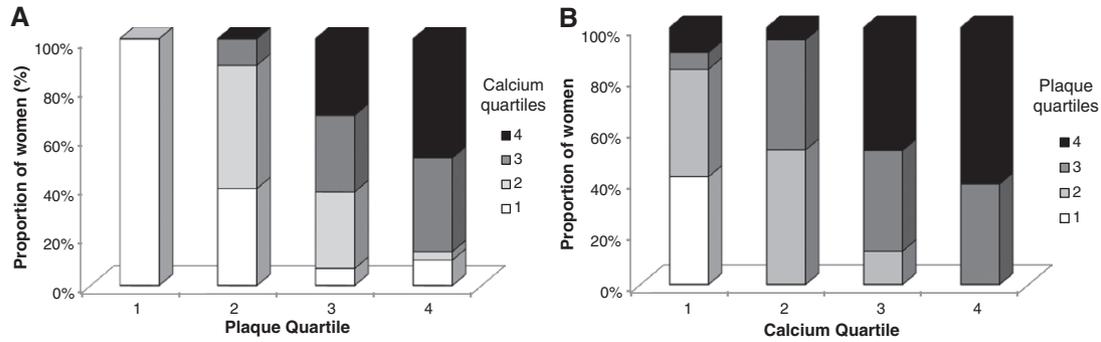


Figure 3. A, Proportion of women with high calcium score (as a function of quartiles 1, 2, 3, and 4) stratified by quartiles of plaque score. B, Proportion of women with high plaque score (as a function of quartiles 1, 2, 3, and 4) stratified by quartiles of calcium score.

correlation between PWV and aortic calcium score. The bivariate analysis showed that >99% of the phenotypic correlation can be attributed to shared genetic effects.

Discussion

To our knowledge, this is the first study to investigate the relation between aortic stiffness and subclinical aortic plaque/calcification using combined CT/MR imaging. A major finding of the present study is that aortic plaque and calcification were highly prevalent in apparently healthy postmenopausal women; prevalence increased with age and was higher in the abdominal compared with the thoracic aorta. There was a close correlation between calcification and plaque, with calcification rarely seen in the absence of plaque. However, the converse was not true: a substantial proportion of women with absent or low calcification scores had a relatively high plaque burden.

The major objective of the present study was to examine the relationship of aortic stiffness to aortic plaque and calcification. Previous studies demonstrating an association between aortic stiffening and atherosclerosis, and between aortic stiffness and calcification, have not distinguished between calcified and noncalcified atheromatous plaque or between calcification in the presence and absence of plaque.^{5,20} In large

epidemiological studies, aortic PWV is not associated with risk factors for atherosclerosis other than age and blood pressure²¹ and is not associated with early stages of atherosclerosis in primate models.⁸ By contrast, animal models of medial calcification results in increased aortic stiffness independently of development of atherosclerosis.⁹ This raises the question as to whether arterial stiffening relates to arterial calcification rather than noncalcified atherosclerotic plaque. Ultrasonic characterization of plaque in the carotid and femoral arteries supports this view with aortic PWV related to echogenic, but not echolucent, plaque.^{10,22} However, ultrasonic measures in these more peripheral arteries provide limited measures of arterial calcification that may not be relevant to the aorta. The present study thus provides the first direct measure of the relation between aortic PWV, atherosclerotic plaque, and calcification. We found no association of aortic PWV with plaque measured along the length of the aorta. By contrast, aortic PWV was associated with aortic calcification. These findings are thus consistent with the animal studies and indirect evidence from human studies which suggest that aortic stiffness is determined mainly by calcification rather than by plaque burden alone.^{8-10,22} Although animal models of calcification suggest that calcification is the cause of arterial stiffening, this cannot be concluded from the present study; it is possible that hemodynamic forces associated with arterial stiffening are responsible for calcification, rather than the reverse.²³ The findings of the present study suggest that the prognostic impact of aortic stiffening is unlikely to be a result of it being a marker for atherosclerotic plaque. Rather, the increased risk of aortic stiffening is likely a result of its adverse hemodynamic effects with respect to pulsatile load on the heart and arteries, where plaque rupture may

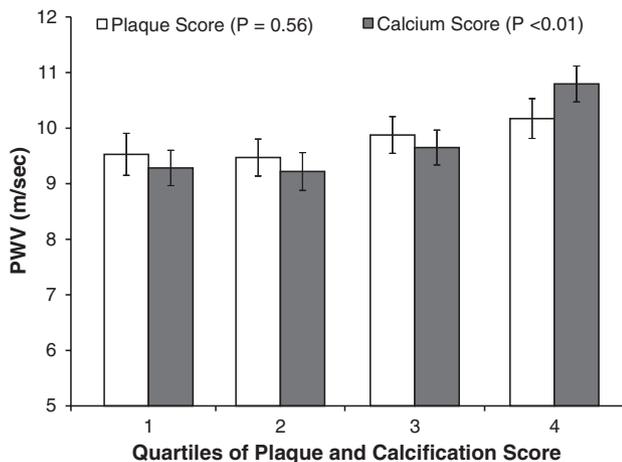


Figure 4. Mean values of pulse wave velocity as a function of quartiles of plaque and calcium score, adjusted for age, mean arterial pressure, antihypertensive, and lipid-lowering therapy. Bars represent standard error.

Table 2. Relation of Pulse Wave Velocity to Age, Blood Pressure, and Calcium Score by Multivariable Linear Regression Analysis

Variable	β	P-Value
Age	0.32	<0.01
MAP	0.30	<0.0001
Heart rate	0.30	<0.01
Calcium score	0.29	<0.01
R^2	0.41	

β indicates standardized regression coefficient; and MAP, mean arterial pressure.

Table 3. Intraclass Correlation Coefficients (ICC) and Heritability by Structural Equation Modelling

Variable	ICC		Model	ACE Estimates		
	MZ (95% CI)	DZ (95% CI)		A (95% CI)	C (95% CI)	E (95% CI)
Plaque score	0.63 (0.29–0.83)	0.34 (–0.06–0.65)	ACE	0.69 (0.00–0.85)	0.00 (0.00–0.47)	0.31 (0.15–0.66)
			AE	0.69 (0.36–0.85)	...	0.31 (0.15–0.64)
Plaque score (age adjusted)	ACE	0.41 (0.00–0.73)	0.00 (0.00–0.38)	0.59 (0.27–1.00)
			AE	0.41 (0.00–0.73)	...	0.59 (0.27–1.00)
Calcium score	0.80 (0.58...0.91)	0.44 (–0.06–0.71)	ACE	0.83 (0.31–0.92)	0.00 (0.00–0.47)	0.17 (0.09–0.35)
			AE	0.83 (0.65–0.92)	...	0.17 (0.09–0.35)
Calcium score (age adjusted)	ACE	0.77 (0.32–0.89)	0.00 (0.00–0.35)	0.23 (0.11–0.49)
			AE	0.77 (0.51 - 0.89)	...	0.23 (0.11–0.49)

A indicates additive genetic; C, shared environment; CI, confidence intervals; DZ, dizygotic; E, nonshared environment; ICC intraclass correlation coefficient; and MZ, monozygotic.

cause thrombosis and tissue infarction.^{24,25} Calcification within the aorta may thus have more important adverse consequences in comparison with calcification within other arteries where, for an equivalent plaque burden, it may even be a marker for plaque stability, and hence associated with lower risk.²⁴

The twin design of this study allowed us to examine the heritability of aortic plaque and calcification. Although confidence limits for estimates of heritability are relatively wide, results of the analysis are consistent with high heritability of aortic calcification, but only modest heritability of plaque burden. These findings suggest that calcification has an important genetic component and are consistent with findings from family studies.²⁶ Furthermore, the phenotypic correlation between arterial stiffness and calcification is explained by a common genetic influence.¹⁰ By contrast, environmental factors were a more important determinant of noncalcified plaque, suggesting that arterial stiffness and calcification have important genetic determinants that may be distinct from those of atherosclerosis.¹⁰ This does not preclude a permissive role for atherosclerosis in calcification and, indeed, such a role would be consistent with the association of calcification with atherosclerotic plaque.

Study Limitations

This study is limited to female twins from the Twins UK cohort. However, this cohort has previously been shown to be comparable with women in the general UK population for disease and lifestyle characteristics. Furthermore, the all-cause and cardiovascular mortality of twins are comparable with that of the general population.^{12,27} Although a degree of error may occur in image coregistration, this would be unlikely to alter the major conclusion of the present study. The study addresses calcification in the aorta and is unlikely to be relevant to calcification in other vascular beds (eg, coronary). The cross-sectional nature of the study limits conclusions on causality. Future prospective and interventional studies will be required to define the clinical implications of plaque and calcium burden in the aorta.

Perspectives

Arterial stiffness is an important predictor of cardiovascular events. However, the pathophysiology of aortic stiffening and

the mechanism by which it relates to cardiovascular events remain unknown. It has been assumed that arterial stiffness is a marker of atherosclerosis along the aorta. However, our findings suggest that it relates to calcification rather than atherosclerotic plaque burden, and the association of arterial stiffness with calcification may be driven by common genes. These observations also suggests that the prognostic importance of PWV is unlikely to be due to it being a marker of degree of atherosclerosis but to adverse hemodynamic consequences of stiffening. Increased pulsatility may increase load on the left ventricle and predispose to plaque rupture in coronary, carotid, and cerebral arteries.

Conclusions

In conclusion, aortic calcification and atherosclerotic plaque are highly prevalent in apparently healthy postmenopausal women. Aortic stiffening relates to calcification independently of plaque burden, and the association of aortic stiffness with calcification is driven by common genes.

Sources of Funding

This work was supported by a British Heart Foundation Project Grants PG/06/032 and SP/12/4/29573. The Twins UK study was funded by the Wellcome Trust; European Community's Sixth and Seventh Framework Programmes (FP-6/2005–2008) LIFE SCIENCES & HEALTH (Ref 005268), EuroClot Consortium (FP7/2007–2013), and ENGAGE project HEALTH-F4-2007 to 201413 and the FP-5 GenomEUtwin Project (QLG2-CT-2002-01254). The authors acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Center award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. T.D.S. is an NIHR senior Investigator.

Disclosures

None.

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Novelty and Significance

What Is New?

- Aortic stiffening relates to calcification, but not plaque, along the length of the aorta; the association of aortic stiffness with calcification is driven by common genes.

What Is Relevant?

- Genetic causes of arterial calcification may underlie the association of aortic stiffening with cardiovascular events, and these likely arise as a

result of the adverse hemodynamic consequences of aortic stiffening, rather than it being a marker of noncalcified atherosclerotic disease.

Summary

Aortic calcification and atherosclerotic plaque are highly prevalent in apparently healthy postmenopausal women. Aortic stiffening relates to calcification independently of plaque burden and the association of aortic stiffness with calcification is driven by common genes.