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Aortic Calcification Is Associated With Aortic Stiffness and Isolated Systolic Hypertension in Healthy Individuals

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Abstract—Arterial stiffening is an independent predictor of mortality and underlies the development of isolated systolic hypertension (ISH). A number of factors regulate stiffness, but arterial calcification is also likely to be important. We tested the hypotheses that aortic calcification is associated with aortic stiffness in healthy individuals and that patients with ISH exhibit exaggerated aortic calcification compared with controls. A total of 193 healthy, medication-free subjects (mean age \pm SD: 66 \pm 8 years) were recruited from the community, together with 15 patients with resistant ISH. Aortic pulse wave velocity (PWV) was measured noninvasively, and aortic calcium content was quantified from high-resolution, thoraco-lumbar computed tomography images using a volume scoring method. In healthy volunteers, calcification was positively and significantly associated with aortic PWV ($r=0.6$; $P<0.0001$) but was not related to augmentation index or brachial PWV. Calcification was significantly higher in treatment-resistant and healthy subjects with ISH compared with controls (mean [interquartile range]: 1.92 [1.14 to 3.66], 0.84 [0.35 to 1.75], and 0.19 [0.1 to 0.78] cm^3 , respectively; $P<0.0001$ for both). In a multiple regression model, aortic calcium was independently associated with aortic PWV along with age, mean arterial pressure, heart rate, and estimated glomerular filtration rate ($R^2=0.51$; $P<0.0001$). Only age, calcium phosphate product, and aortic PWV were independently associated with calcification. These data suggest that calcification may be important in the process of aortic stiffening and the development of ISH. Calcification may underlie treatment resistance in ISH, and anticalcification strategies may present a novel therapy. (*Hypertension*. 2009;53:524-531.)

Key Words: calcium ■ artery ■ stiffness ■ aorta ■ hypertension

In almost all societies, there is progressive stiffening of the large elastic arteries with age, resulting in a widening of pulse pressure.^{1,2} Ultimately, this leads to the development of isolated systolic hypertension (ISH), which is now the most common form of hypertension in the United States and United Kingdom, affecting approximately half of those aged >60 years.³ A widened pulse pressure, particularly in the central arteries, leads to left ventricular hypertrophy and increases the risk of stroke and myocardial infarction. Arterial stiffening, per se, is also an important determinant of cardiovascular risk. Indeed, aortic pulse wave velocity (aPWV), the current “gold-standard” measure of stiffness, predicts future cardiovascular events in a variety of populations, including unselected older adults, diabetics, and hypertensives, independent of blood pressure.⁴

The precise mechanisms responsible for arterial stiffening are incompletely understood but are thought primarily to involve structural changes within the media, such as fatigue fracture of elastin and deposition of collagen.⁵ An emerging

additional mechanism is arterial calcification.⁶ This may occur in the intima, in conjunction with atherosclerotic plaques, or in the media as arteriosclerosis. Although there is an association between the 2 processes, they are pathologically distinct.^{7,8} Moreover, there is only a modest correlation between atherosclerotic burden and aortic stiffness.⁹ In animals, drug-induced vascular calcification leads to aortic stiffening and the development of an ISH phenotype.^{10,11} In humans, ageing is associated with aortic stiffening² and medial calcification.^{12,13} Aortic calcification is associated with left ventricular hypertrophy¹⁴ and increased cardiovascular risk,^{15,16} and calcification is more common in individuals with hypertension, diabetes mellitus, or renal failure.^{17,18} Interestingly, several studies have reported a positive association between arterial calcification and aPWV in subjects with chronic kidney disease (CKD).^{19–21} However, the relationship between arterial calcification and aortic stiffness in the general population remains unclear.

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We hypothesized that aPWV is independently related to the degree of aortic calcification in healthy individuals and that subjects with ISH, as a model of exaggerated aortic stiffening, would have more extensive aortic calcification than normotensive individuals. The aim of the present study was to test this hypothesis in a community-based cohort of unselected healthy subjects, without manifest cardiovascular disease, and a cohort of treatment-resistant systolic hypertensives, as a model of extreme arterial stiffening, using 16-section computed tomography (CT) for accurate quantification of aortic calcification.

Methods

Subjects

A total of 200 healthy subjects were recruited from the Anglo Cardiff Collaborative Trial, an ongoing, community-based investigation into the factors influencing arterial stiffness.² Individuals were selected at random from local general practice lists by letter of invitation (the overall response rate was 85%). Subjects with diabetes mellitus, hypercholesterolemia (self-reported or total cholesterol ≥ 6.5 mmol/L), renal disease (defined as a clinical history, creatinine ≥ 150 $\mu\text{mol/L}$, or an active urinary sediment), a history of cardiovascular disease (defined as a clinical history or evidence on examination), known inflammatory conditions, malignancy, or a recent history of infection were excluded from the present analyses, as were subjects receiving any medication. In addition, 15 subjects with treatment-resistant ISH were recruited from the hypertension clinics at Addenbrooke's Hospital. This was defined as a documented history of ISH and failure to achieve the current British Hypertension Society target of $< 140/85$ mm Hg despite therapy with ≥ 3 antihypertensive drugs, including a thiazide diuretic, calcium channel antagonist, and renin-angiotensin blocker. Approval was obtained from the Local Research Ethics Committee, and written informed consent was obtained from each participant.

Hemodynamics

Seated peripheral blood pressure was recorded in the brachial artery using a validated oscillometric technique (HEM-705CP; Omron Corporation). Radial artery waveforms were then recorded with a high-fidelity micromanometer (SPC-301; Millar Instruments) from the wrist of the same arm. Pulse wave analysis (SphygmoCor; AtCor Medical) was then used to generate a corresponding central (ascending aortic) waveform using a generalized transfer function,²² which has been prospectively validated for the assessment of ascending aortic blood pressure.^{23,24} Augmentation index (AIx), a composite measure of wave reflection; the height of the first systolic peak or shoulder; wave travel time, time to the inflection point of the central waveform; and heart rate were determined using the integral software. Reflection time was defined as wave travel time divided by 2, and reflection distance was estimated as aPWV multiplied by reflection time.²⁵ Mean arterial pressure (MAP) was calculated from integration of the radial artery waveform. The aPWV was measured using the same device by sequentially recording ECG-gated carotid and femoral artery waveforms²⁶ and brachial pulse wave velocity (bPWV) from carotid and radial arteries.²⁶ All of the measurements were made in duplicate, and mean values were used in the subsequent analysis.

CT Imaging

The entire aorta was visualized by obtaining 1.5-mm-thick slices through the thorax, abdomen, and pelvis with unenhanced helical CT (16-slice Siemens Medical Solutions system, Forchheim; total dose: < 8 mSv). Analysis was conducted offline using a Leonardo workstation with Syngo software. The degree of calcification was determined at 3 sites: the ascending aorta (valve to left subclavian); descending thoracic aorta (left subclavian to diaphragm); and within a defined section of abdominal aorta. Calcium quantification at the



Figure 1. A section through the abdomen illustrating calcification within the aorta (white).

first 2 sites was subjectively assessed by 2 trained observers who graded calcification as no calcium present, flecks, moderate, or confluent.²⁷ This approach, which has been widely used,^{19,20,28} was adopted because of the substantial curvature of the aorta in the thorax, movement with respiration, and sparse amounts of calcium, mainly as flecks, which are not well registered by the automated software. In the abdominal aorta, an objective volume scoring method included in the system software was used. The number of voxels ≥ 130 HU within the wall of the aorta was determined along a 5-cm segment just proximal to the bifurcation, which gave a score in cubic centimeters (Figure 1). This is a validated and accurate technique that compares favorably with electron beam CT,^{29,30} and we have shown previously that this technique has excellent within- and between-observer repeatability.³¹

Protocol

Height and weight were assessed. After 5 minutes seated rest, blood pressure and radial artery waveforms were recorded. Subjects then rested supine for 15 minutes, after which brachial blood pressure, aPWV, and bPWV were recorded. Twenty mL of blood were drawn from the antecubital fossa into plain tubes. The samples were centrifuged at 4°C (4000 rpm for 20 minutes) and the serum separated and stored at -80°C for subsequent analysis. Electrolytes, cholesterol, triglycerides, glucose, C-reactive protein (CRP), and parathyroid hormone were determined using standard methodology in an accredited laboratory. Estimated glomerular filtration rate (eGFR) was determined using the modified Modification of Diet in Renal Disease formula. Subjects then underwent CT.

Data Analysis

Data were analyzed using SPSS software (version 15.0). When the distribution of variables was significantly skewed (creatinine, eGFR, CRP, parathyroid hormone, aPWV, and abdominal calcium score), natural logarithmic transformations were applied before analysis. Comparisons between groups were made using Student's *t* tests or ANOVA with Bonferroni corrections. Stepwise multiple linear regression was performed to investigate the independent predictors of aPWV and calcification. Variables entered into the model were chosen if significantly associated in simple correlation analyses and those variables known or previously associated with the dependent variable from published observations. Values represent means \pm SDs or medians (interquartile range), and a *P* value of < 0.05 was considered significant.

Results

Healthy Volunteers

Of the 200 healthy subjects recruited, data from 193 individuals were available for analysis (7 were excluded

Table 1. Characteristics of the Healthy Subjects (n=193)

Parameter	Value
Age, y	66±8
Gender, male/female	99/94
Height, m	1.66±0.09
Weight, kg	75±14
Seated SBP, mm Hg	140±19
Seated DBP, mm Hg	83±11
Heart rate, bpm	74±13
Total cholesterol, mmol/L	5.3±1.1
Triglycerides, mmol/L	1.7±1.0
Glucose, mmol/L	5.2±0.8
Creatinine, μmol/L	72 (60 to 85)
eGFR, mL/min per 1.73 m ²	83 (63 to 121)
CRP, mg/L	2.28 (1.00 to 4.03)
Calcium, mmol/L	2.2±0.1
Phosphate, mmol/L	1.1±0.2
PTH, pmol/mL	2.97 (2.23 to 4.18)

Data are means±SDs or medians (interquartile range). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone.

because of the presence of atrial fibrillation, malignancy on imaging, or the inability to complete the CT protocol). The mean age of the cohort was 66 years (range: 51 to 92 years). There was a roughly equal gender distribution, and 21 subjects were current cigarette smokers and 75 were ex-smokers. Based on seated blood pressure readings, 114 subjects were classified as normotensive (<140/90 mm Hg), 61 met the criteria for ISH (≥140 and <90 mm Hg), and 18 had mixed systolic/diastolic hypertension (≥140 and ≥90 mm Hg). The demographics of the whole healthy cohort (ie, normotensive subjects and untreated systolic and mixed hypertensives) are presented in Table 1, and detailed supine hemodynamic and imaging data are presented in Table 2.

Table 2. Hemodynamic and Imaging Data From the Healthy Subjects (n=193)

Parameter	Value
Supine SBP, mm Hg	134±21
Supine DBP, mm Hg	78±10
Supine MAP, mm Hg	98±13
Heart rate, bpm	74±13
Central supine SBP, mm Hg	126±18
Central supine DBP, mm Hg	79±10
Aix, %	31±9
aPWV, m/s	9.1 (7.9 to 10.7)
bPWV, m/s	8.6 (7.8 to 9.6)
Ascending aortic calcification, AU	0.22±0.56
Descending aortic calcification, AU	0.81±0.83
Abdominal aortic calcification, cm ³	0.53 (0.04 to 1.65)

Data are means±SDs or medians (interquartile range). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; AU, arbitrary units.

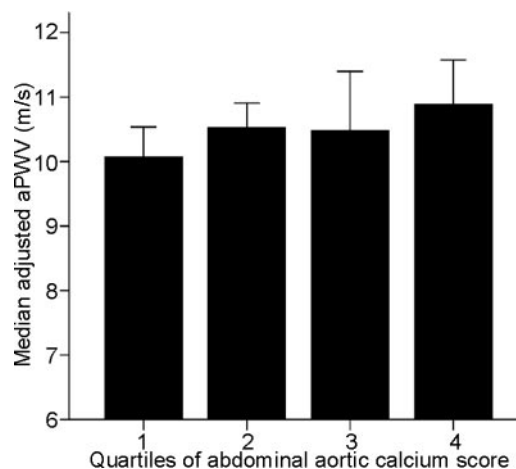


Figure 2. Median aPWV as a function of quartiles of abdominal aortic calcium score for all of the healthy subjects. aPWV has been adjusted for age and MAP. Bars represent the 95% confidence of the distribution (n=193); $P=0.014$ ANOVA.

There was a significant correlation between abdominal aortic calcification score with that in the ascending ($r=0.3$; $P=0.001$) and descending ($r=0.6$; $P<0.001$) thoracic aorta. Calcification at all 3 of the sites was positively correlated with aPWV, but the strongest correlation was with abdominal calcium score ($r=0.4$; $P<0.001$), followed by descending thoracic ($r=0.4$; $P<0.001$) and then ascending aorta ($r=0.2$; $P=0.008$). Division of the cohort into quartiles of abdominal calcification score suggested a dose-response relationship with aPWV, which persisted even after adjusting for age and MAP ($P=0.014$; Figure 2). Neither bPWV ($r=0.1$; $P=0.2$) nor Aix ($r=-0.1$; $P=0.5$) was significantly related to calcium score at any site. However, peripheral pulse pressure was positively correlated with abdominal ($r=0.3$; $P=0.001$), descending ($r=0.2$; $P=0.003$) and ascending ($r=0.2$; $P=0.04$) thoracic calcium scores, and this remained significant after adjustment for age, MAP, gender, smoking, and height. Central pulse pressure was also correlated with calcium score in the descending and abdominal aorta sites, but to a lesser degree, and this was not significant after adjustment.

The aPWV was also positively correlated with age, male gender, weight, cigarette smoking, MAP, heart rate, serum creatinine, and CRP and inversely with eGFR. Therefore, stepwise multiple regression was used to determine the independent predictors of aPWV. Abdominal calcium score was used for the models, because it had the strongest bivariate correlation with aPWV. In a simple model, abdominal aortic calcium score alone explained 17% of the variance in stiffness (Table 3, model 1). The addition of age, MAP, and gender improved the R^2 to 41%, and calcification remained positively associated with aPWV (Table 3, model 2). Finally, all of the univariate correlates of aPWV (but eGFR rather than creatinine), together with height, total cholesterol, triglycerides, and glucose, were included in a stepwise model. This increased the R^2 to 51%, but only age, MAP, eGFR, heart rate, and aortic calcium score remained independent predictors of aPWV (Table 3, model 3). Substitution with ascending or descending thoracic calcium score reduced the

Table 3. Multivariate Models for aPWV

Variable	Regression Coefficient±SE	β	R^2 Change	<i>P</i>
Model 1 ($R^2=0.17$; $P<0.001$)				
Ln aortic calcification, cm^3	0.07±0.01	0.41		<0.001
Model 2 ($R^2=0.41$; $P<0.001$)				
Age, MAP, gender			0.37	<0.001
Ln aortic calcification, cm^3	0.31±0.12	0.20	0.04	0.008
Model 3 ($R^2=0.51$; $P<0.001$)				
MAP, mm Hg	0.08±0.01	0.40	0.22	<0.001
Age, y	0.01±0.03	0.32	0.18	<0.001
Heart rate, bpm	0.01±0.01	0.30	0.07	<0.001
Ln aortic calcification, cm^3	0.01±0.01	0.15	0.03	0.03
Ln eGFR, mL/min per 1.73 m^2	-0.08±0.04	-0.14	0.01	0.04

Excluded were height, weight, cholesterol, triglycerides, glucose, smoking, gender, and ln CRP. aPWV was log transformed for this analysis. Ln indicates log normal.

R^2 of the models, and when all 3 of the calcium scores were included, only abdominal calcification remained independently associated with aPWV. Stratifying the analysis by gender or substituting individual lipid subfractions did not alter the associations (data not shown). Rerunning the models for just the normotensive or untreated hypertensive healthy subjects slightly reduced the R^2 values, as might be expected, but did not meaningfully alter any of the associations or the strength of the relationship with vascular calcification.

Aortic calcification was positively associated with age, male gender, serum creatinine, glucose, and aPWV and inversely with eGFR. However, there was no significant relationship with the calcium phosphate product (or concentrations of individual ions), serum parathyroid hormone, or CRP levels. Multivariate analysis revealed that only age, calcium phosphate product, and aPWV were independently associated with aortic calcification (Table 4).

ISH and Aortic Calcification

To test the hypothesis that ISH is associated with exaggerated aortic calcification, 2 subsets of healthy subjects were iden-

Table 4. Multivariate Model for Abdominal Aortic Calcification

Variable	Regression Coefficient±SE	β	<i>P</i>
$(R^2=0.37, P<0.001)$			
Age, y	0.08±0.02	0.46	<0.001
Ln aPWV	1.53±0.57	0.28	0.008
Calcium phosphate product	0.79±0.36	0.22	0.03

Calcium score was log transformed for the analysis, as was the aPWV. Excluded variables were height, weight, gender, cholesterol, triglycerides, glucose, ln eGFR, ln CRP, ln parathyroid hormone, and smoking (all $P>0.2$). Ln indicates log normal.

tified: those who were normotensive ($n=114$) and those with a confirmed diagnosis of ISH ($n=61$), defined as a seated systolic blood pressure ≥ 140 and diastolic <90 mm Hg on 3 occasions. An additional 15 individuals with treatment-resistant ISH were studied; other than taking a thiazide diuretic, angiotensin-converting enzyme inhibitor, and a calcium channel antagonist, 6 subjects were also receiving a β -blocker, 2 an α -blocker, and 1 spironolactone. The characteristics and hemodynamic data for the 3 groups are presented in Table 5.

As expected, healthy subjects with ISH had a higher aPWV, even after adjustment for MAP, than healthy normotensives, but there was no difference in AIX. Reflection distance and the height of the first systolic peak or shoulder were increased in those with ISH, and reflection time was reduced. They also had more extensive abdominal and descending thoracic aortic calcification than controls. Both of these differences were exaggerated in the resistant hypertensives (Figure 3). The difference in abdominal aortic calcification persisted after correcting for age or age², gender, MAP, smoking status, and creatinine (data not shown). There was no difference in biochemical parameters other than serum creatinine between the groups.

Discussion

Aortic stiffness is an important, independent predictor of future cardiovascular risk in unselected older individuals. However, the mechanisms underlying aortic stiffening are incompletely understood. The aim of this study was to explore the relationship between aortic stiffness and calcification in healthy subjects using quantitative, high-resolution CT imaging and aPWV, the current gold-standard measure of arterial stiffness. The main novel findings were that calcification in all regions of the aorta was positively correlated with aPWV and that this relationship remained significant after controlling for potential confounding influences. Aortic calcification was also related to peripheral but not to central pulse pressure or indices of wave reflection. Finally, we demonstrated that ISH is associated with increased calcium deposition in the aorta and that this is most marked in individuals who are resistant to antihypertensive therapy.

Calcification of the large arteries in humans is well recognized, particularly with ageing,^{12,13,32,33} CKD,¹⁶ and diabetes mellitus.³⁴ The impact of calcification on systemic hemodynamics and aortic stiffness has largely been explored in subjects with CKD. However, the majority of these studies have only assessed calcification in one particular aortic segment or used subjective measures of calcification based on plain radiographs and/or ultrasound. Guerin et al¹⁹ reported a positive association between a composite ultrasound-based calcium score (abdominal aorta, ilio-femorals, legs, and common carotid arteries) and aPWV in hemodialysis patients. They went on to show that the presence of intimal and medial calcification, in such patients, independently predicts mortality and morbidity.¹⁶ Using CT, 2 other groups have demonstrated a correlation between aPWV and abdominal calcium score in patients with CKD.^{21,35} Interestingly, Raggi et al²⁰ reported that the abdominal but not the thoracic calcium score was independently related to aortic stiffness in hemodialysis patients. However, abdominal calcification was assessed by

Table 5. Characteristics of the Normotensive and ISH Subjects

Parameter	Healthy (n=114)	ISH (n=61)	Resistant ISH (n=15)	P
Age, y	65±8	68±8*	74±8*	<0.001
Gender, male/female	58/56	30/31	6/9	0.7
BMI, kg/m ²	26.5±4.7	27.8±4.6	26.8±3.6	0.2
Smoker, n	12	7	0	0.4
Seated SBP, mm Hg	128±12	154±11	156±16	
Seated DBP, mm Hg	79±9	85±8	80±9	
Heart rate, bpm	72±12	76±12	72±14	0.1
Supine MAP, mm Hg	92±9	103±9*	106±11*	<0.001
Aix, %	31±10	31±9	34±6	0.5
P1, mm Hg	103±10	118±10*	119±12*	<0.001
Reflection distance, mm	594±140	713±181*	754±197*	<0.001
Reflection time, ms	68±7	65±5*	66±5	0.025
aPWV, m/s	8.4 (7.4 to 9.7)	10.6 (8.7 to 12.2)*	10.8 (10.0 to 14.0)*	<0.001
Adjusted aPWV, m/s†	8.8 (7.8 to 10.2)	9.5 (7.8 to 11.5)*	10.7 (8.9 to 14.7)*	<0.001
AA calcium, AU	0.22±0.58	0.21±0.52	0.33±0.50	0.8
DA calcium, AU	0.56±0.78	0.97±0.88*	1.67±0.71*	<0.001
Abdo calcium, cm ³	0.19 (0.10 to 0.78)	0.84 (0.35 to 1.75)*	1.92 (1.14 to 3.66)*	<0.001
Creatinine, μmol/L	70 (51 to 81)	76 (61 to 96)	84 (69 to 71)	0.06
eGFR, mL/min per 1.73 m ²	84 (66 to 128)	83 (52 to 118)	78 (60 to 87)	0.07

Data are means±SDs or medians (interquartile range). BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; P1, height of first systolic peak; AA, ascending aortic; DA, descending aortic; Abdo, abdominal aortic. Overall differences among the 3 groups are indicated in the final column (ANOVA).

*Significant differences on posthoc testing (Bonferroni) between normotensive and healthy ISH subjects or between normotensive and resistant ISH subjects are indicated in the respective columns.

†Data are adjusted for MAP.

plain radiography, whereas thoracic deposition was quantified by electron beam CT. Sigrist et al³⁶ demonstrated a positive association between changes in arterial calcification and aPWV in subjects with CKD over a 2-year period, suggesting a potential causal relationship. However, they assessed calcium deposition in the superficial femoral artery rather than in the aorta. In healthy subjects, one small study has reported a relationship between brachial-ankle pulse

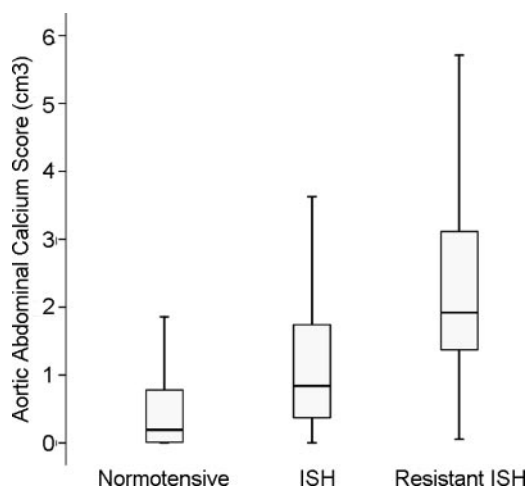


Figure 3. A box-and-whisker plot of abdominal aortic calcium score in normotensive and hypertensive individuals. Error bars encompass all of the data, the line represents the median, and the box the interquartile range. $P<0.0001$ for trend.

wave velocity and the length of calcified abdominal aorta on plain radiographs in Japanese subjects, but data on aPWV were not available.³⁷ Hypertension has been associated with increased calcification and faster progression of calcification.^{17,18} However, no data concerning calcification and ISH, which can be considered primarily as a disease of arterial stiffening, are available.

We determined aortic calcification at 3 distinct anatomic locations (ascending, descending, and abdominal) using unenhanced CT. This modality allows direct quantification of vascular calcium load and is at least (if not more) as accurate as electron beam CT.²⁹ In the healthy subjects, aPWV was positively correlated with calcification at all 3 of the aortic sites. As expected, aPWV was also related to a number of other variables, including age, MAP, male gender, cigarette smoking, and heart rate.^{2,5} After adjustment for these and other potential factors influencing arterial stiffness, aortic calcium content remained independently correlated with aortic stiffness. In contrast, there was no relationship between calcification and bPWV or Aix, an index of wave reflection. This suggests that aortic calcification is principally associated with localized stiffening of the aorta rather than with systemic changes in more peripheral vessels, or altered wave reflections, which is perhaps unsurprising given the variability with which arteries calcify and vessels stiffen.³⁸

The lack of association between wave reflection and calcification may seem surprising. However, we have dem-

onstrated previously that AIx changes little with age after the 6th decade, despite large changes in aPWV.² One potential explanation for the current observations is that calcification leads to a distal shift in the apparent site of wave reflection. This theory is supported by the longer reflection distance that we observed in subjects with ISH. As such, the faster speed of the reflected wave resulting from the increase in aPWV would be offset by a greater path length, and the net effect would be no change in AIx. Because central systolic pressure is much more dependent on wave reflection than brachial systolic pressure, this would also explain why calcification was only associated with brachial and not aortic pulse pressure. The reasons for the change in reflection distance were not explored but may be a function of preferential stiffening of the elastic arteries, resulting in better impedance matching with the inherently stiffer muscular vessels of the lower limbs.

Although often considered as uniform, the structure and biophysical properties of the aorta change considerably along its length, the abdominal portion being more muscular and less elastic. As such, the pathological processes underlying arterial stiffening may vary from one location to another. The aPWV was most strongly correlated with calcification in the abdominal aorta, which is consistent with the results of Raggi et al²⁰ in hemodialysis patients. This suggests that deposition of calcium in the abdominal aorta has a greater influence on average aortic stiffness than calcification at other locations. Given that the carotid-diaphragm and diaphragm-femoral segments of the overall carotid-femoral pathway are roughly equal in size, calcification appears to have a greater functional impact on biomechanical properties of the abdominal aorta compared with the thoracic portion. Nevertheless, it remains unclear as to which section of the aorta stiffens most with age^{39,40} or the development of ISH, and greater evidence of causality will require regional measurement of aPWV and calcification in the same patients over time.

Among unselected, otherwise healthy individuals, the ISH phenotype was associated with increased aortic stiffness and a greater aortic calcification, extending our previous observations.⁴¹ Both of these differences persisted after adjustment for confounding variables, including MAP, and were much more pronounced in a separate cohort of treatment-resistant subjects with ISH. This suggests that aortic calcification may play an important role in the development of ISH in humans, as is the case in animal models of vascular calcification.¹¹ Moreover, aortic calcification leading to exaggerated aortic stiffening may explain why some individuals with ISH are resistant to antihypertensive drugs, which largely lower blood pressure by peripheral vasodilatation rather than a direct effect on large arteries. Moreover, in CKD, aPWV is an important determinant of the response to antihypertensive therapy, which, in turn, predicts outcome,⁴² suggesting that attenuation of aortic stiffening in ISH may be a valuable additional therapeutic target.

A number of risk factors for arterial calcification have been identified, including age, hypertension, hypercholesterolemia, cigarette smoking, and diabetes mellitus.^{32,33,43} Among CKD patients the duration of dialysis, serum phosphate, and

inflammatory markers also seem important.^{16,19,44} However, the majority of investigators did not use quantitative methods to assess calcification and frequently included patients with manifest cardiovascular disease. Moreover, other than age, many of the other reported associations are relatively modest and vary between gender and study. The only parameters independently related to aortic calcification in the current study, other than aPWV, were age and calcium phosphate product. This may reflect the a priori exclusion of subjects with manifest atherosclerosis, diabetes mellitus, CKD, and those receiving cardiovascular medication. Nevertheless, the multiple regression model in the present study only explained $\approx 40\%$ of the variance in calcification, suggesting that additional factors are involved.

Limitations of the Present Study

The present study design was cross-sectional, and, therefore, it is difficult to determine whether calcification causes arterial stiffening. One counterargument is that aortic stiffening, perhaps by virtue of degeneration of elastin fibers, which are rich in calcium-binding domains, promotes deposition of calcium in the arterial wall and that calcification is simply a bystander to aortic stiffening. Only data from future longitudinal or interventional studies will provide greater evidence of causality. We also assessed total calcification, being unable to distinguish between medial and intimal calcification with CT. Although these are distinct pathological processes, both are linked to aortic stiffening in CKD patients¹⁶ and are thought to have similar effects on the vessel wall.⁴⁵ Moreover, although pathological studies may distinguish between the 2 forms of calcification, they are unable to provide true measures of *in vivo* stiffness. Another potential criticism might be the somewhat subjective assessment of the calcification in the thoracic aorta. The reasons for this approach relate to the fact that there are usually relatively few disjointed flecks of calcification, which makes precise objective assessment open to error, especially given the curvature of the ascending and proximal descending aorta, motion artifacts in the ascending aorta, prominent osteophytes adjacent to the descending aorta, and the variable extent of calcification at the site of the ligamentum arteriosum. However, it is reassuring that the subjective assessments in the thoracic aorta were very much in line with the objective measurements in the standard 5-cm length of abdominal aorta, which, being much straighter, offers reliable³¹ computer-based measurements. Finally, we cannot exclude the possibility that long-term antihypertensive therapy modulates arterial calcification, and the role of calcification in defining the response to antihypertensive medication needs to be further explored in treatment-naïve ISH subjects.

Perspectives

We have demonstrated that aortic calcification is an independent predictor of aortic stiffness and brachial pulse pressure in healthy individuals and that ISH is associated with exaggerated aortic calcification and stiffening. These data imply that aortic calcification may play an important role in arterial stiffening and the development of ISH.

Moreover, the extent of calcium deposition may determine the response to antihypertensive therapy. This may have important implications for the rational design of new therapeutic strategies to treat the large number of older subjects with ISH.

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Disclosures

None.

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