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Aortic stiffness and calcification in men in a population-based international study

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Abstract

Objectives—Aortic stiffness, a hallmark of vascular aging, is an independent risk factor of cardiovascular disease and all-cause mortality. The association of aortic stiffness with aortic calcification in middle-aged general population remains unknown although studies in patients with end-stage renal disease or elderly subjects suggest that aortic calcification is an important determinant of aortic stiffness. The goal of this study was to examine the association of aortic calcification and stiffness in multi-ethnic population-based samples of relatively young men.

Methods—We examined the association in 906 men aged 40–49 (81 Black Americans, 276 Japanese Americans, 258 White Americans and 291 Koreans). Aortic stiffness was measured as carotid-femoral pulse wave velocity (cfPWV) using an automated waveform analyzer. Aortic calcification from aortic arch to iliac bifurcation was evaluated using electron-beam computed tomography.

Results—Aortic calcium score was calculated and was categorized into four groups: zero (n=303), 1–100 (n=411), 101–300 (n=110), and 401+ (n=82). Aortic calcification category had a significant positive association with cfPWV after adjusting for age, race, and mean arterial pressure (mean (standard error) of cfPWV (cm/second) from the lowest to highest categories: 836 (10), 850 (9), 877 (17) and 941 (19), p for trend <0.001). The significant positive association remained after further adjusting for other cardiovascular risk factors. The significant positive association was also observed in each race group.

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Conclusions—The results suggest that aortic calcification can be one mechanism for aortic stiffness and that the association of aortic calcification with stiffness starts as early as the 40's.

Keywords

aortic stiffness; aortic calcification; international multi-ethnic study

Introduction

Aortic stiffness, a hallmark of vascular aging,¹ is recognized as an important prognostic index and potential therapeutic target.² Aortic stiffness is a risk factor for cardiovascular disease (CVD) and all-cause mortality independent of blood pressure (BP) and other CVD risk factors.³ Carotid-femoral pulse wave velocity (cfPWV) is considered to be the gold standard method for assessing aortic stiffness.⁴ The recent European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension suggested the measurement of PWV as a tool for assessment of subclinical organ damage.⁵ cfPWV is strongly associated with age and BP but has little association with low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively).⁶ indicating that aortic stiffness is not driven by the atherosclerotic process especially in its early stage.⁶

Aortic stiffness is caused by structural changes to the aorta, including fragmentation and degeneration of elastin as well as increases in collagen.^{1, 7} An emerging mechanism is aortic calcification. Studies in animals⁸ and in patients with end-stage renal disease^{9, 10} suggest that aortic calcification is an important determinant of aortic stiffness. The Rotterdam Study reported a significant association of cfPWV with calcification of the carotid artery but not the aortic arch.¹¹ Two recent studies reported the significant positive association of cfPWV with aortic calcification: one among 193 healthy elderly volunteers¹² and another among 900 Caucasian women with a mean age of 58 from the Twins UK cohort.¹³ To our best knowledge, no previous population-based study has examined the association of cfPWV with aortic calcification in younger age groups or multi-ethnic cohorts. The aim of the study was to investigate the association of cfPWV with aortic calcification in population-based samples of Black, Japanese, and White American men as well as Korean men from the electron-beam computed tomography and risk factor assessment in Japanese and US men in the post-World War II birth cohort (ERA JUMP) study.

Materials and Methods

Subjects

The ERA JUMP study is a population-based study in men aged 40–49 without cardiovascular or other severe disease at baseline during 2002 to 2006 as previously described.^{14–16} The study examined 107 Black and 310 White Americans in Allegheny County, Pennsylvania, US, 310 Japanese in Kusatsu, Shiga, Japan, 303 Japanese Americans in Honolulu, Hawaii, US, and 302 Koreans in Ansan, South Korea. In Allegheny County, Pennsylvania, Black and White American participants were randomly selected based on the voter's registration list.^{14, 16} In Kusatsu, Shiga, Japan, Japanese participants were randomly selected, based on the Basic Residents' Register of the city.¹⁴ In Honolulu, Hawaii, Japanese American participants were randomly selected from a representative sample of offspring of fathers who participated in the Honolulu Heart Program.¹⁴ In Ansan, South Korea, Korean participants were randomly selected from the Korean Health and Genomic Study, an ongoing-population-based prospective cohort study.¹⁵ The present study excluded Japanese in Japan because we did not measure cfPWV in them. Additionally we excluded 116 subjects (11%) who had missing data of either cfPWV (n=75) or aortic calcification (n=41). The total number for the present study was 906 (81 Black Americans, 276 Japanese

Americans, 291 Koreans, and 258 White Americans.) Informed consent was obtained from each participant. The study protocol was approved by the Institutional Review Boards of University of Pittsburgh, Pittsburgh, US, Korea University, Seoul, South Korea, Kuakini Medical Center, Honolulu, US, and Shiga University of Medical Science, Otsu, Japan.

All participants underwent a physical examination, lifestyle questionnaire, and laboratory assessment as described previously.¹⁴ Pack-years of smoking were calculated as years of smoking multiplied by the number of cigarettes per day divided by 20. Alcohol drinkers were defined as those who drank alcohol two days per week. Diabetes mellitus was defined as fasting serum glucose level ≥ 7 mmol/L or use of anti-diabetic medications. Venipuncture was performed early in the clinic visit after a 12-hour fast. Serum samples were stored at -80°C , shipped on dry ice to University of Pittsburgh, and determined for levels of LDL-C, HDL-C, triglycerides, and glucose.

BP and heart rate were measured in the right arm of the seated participant after the participant emptied his bladder and sat quietly for five minutes, using an appropriate-sized cuff, with an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan).¹⁴ The average of two measurements was used. Mean arterial pressure (MAP) was calculated as $1/3$ (systolic BP – diastolic BP) + diastolic BP.

cfPWV

Before the study started, staff at the Ultrasound Research Laboratory, University of Pittsburgh visited to Honolulu to train the sonographers in Honolulu and from South Korea for PWV measurements. PWV measures were automatically generated using a noninvasive and automated waveform analyzer (VP2000, Omron, Japan).¹⁷ This device recorded the carotid and femoral pulse waveform using multi-array tonometers. It also recorded the phonocardiogram, ECG, and volume pulse form and arterial BP at brachial and tibial arteries in both sides. Following 10 minutes of rest in a supine position, the participant had occlusion and monitoring cuffs placed around both arms and ankles. The arm cuffs were placed on bare arms or over light clothing, and the ankle cuffs were placed on bare ankles. ECG electrodes were placed on both wrists and a phonocardiogram, a microphone for detecting heart sounds, was placed on the left edge of sternum. The cuffs were connected to a plethysmographic sensor that determined volume pulse form and to an oscillometric pressure sensor that measured BP. The pulse volume waveforms were recorded using a semiconductor pressure sensor. Carotid and femoral waveforms were obtained simultaneously. Sonographers palpated the left femoral artery and the left carotid artery and placed the handheld tonometers over these two pulse areas to obtain femoral and carotid pulse waveforms simultaneously. A foot-pedal was used to start the recording. Data were collected two times for each participant and the values were averaged. cfPWV was calculated by time-phase analysis using volume waveforms of respective arteries (carotid and femoral arteries.) PWV was calculated as (Distance between arterial sites)/(Time between the foot of the respective waveforms). Distance was measured over the surface of the body. Intra-class correlation for re-examination was 0.84.

Aortic calcification

The scanning was performed using a GE-Imatron C150 EBT scanner (GE Medical Systems, South San Francisco, U.S.) at the three centers using standardized methods. For evaluating aortic calcification, 6-mm contiguous images of the aorta were obtained from the aortic arch to the iliac bifurcation using a 300-millisecond exposure time. All scan data were saved to optical disc and shipped to the Cardiovascular Institute, University of Pittsburgh Medical Center for evaluation. One trained reader blinded to participant's characteristics and the study centers, read the image. Calcification was considered present in the aorta when at least

3 contiguous pixels of 130 Hounsfield Unit were present on a 30-cm matrix. Aortic calcium score was calculated by the widely-accepted Agatston method.¹⁸ The intraclass correlation of re-read for the non-zero aortic calcium score is 0.99.¹⁹

Statistical analyses

The distribution of aortic calcium score was highly rightly skewed and about a third had a value of zero. Thus we categorized aortic calcium score into four groups: zero, 1–100, 101 to 400, and 400+. Associations of cfPWV with the aortic calcification category were evaluated using general liner model analyses. For the multivariable adjustment, model 1 included age, race, and MAP; model 2 = model 1 plus body-mass index (BMI), pack-years of smoking, diabetes, and medications for hypertension; model 3 = model 2 plus LDL-C, HDL-C, triglycerides, and medication for hyperlipidemia. These model selections were based on a recent systemic review.⁶ Additionally, associations of cfPWV with aortic calcium score were evaluated using multiple linear regression analyses. For the analyses, we excluded individuals with aortic calcium score = zero and then log-transformed aortic calcium score. Adjustments were made in the same way as described above. Race-specific associations of cfPWV with the aortic calcification category were evaluated using general liner model analyses. Adjustments were made in the same way as described above except for race in model 1. P values of less than 0.05 were considered to indicate statistical significance. All analyses were performed with the use of PASW statistics 18 (IBM).

Results

Of all subjects prevalence of aortic calcium score >0, 100, and 400 was 66.6%, 21.2 % and 9.1 %, respectively. Aortic calcium scores at 25th, 50th, 75th, 90th, 95th percentiles were 0, 9.0, 64.3, 357.5, and 744.6, respectively. The category of aortic calcification had significant positive associations with cfPWV (Figure) as well as age, MAP, BMI, pack-years of smoking, diabetes, medications for hypertension and hyperlipidemia (Table 1). The category of aortic calcification had no significant association with LDL-C or HDL-C.

cfPWV had significant positive associations with the aortic calcification category after adjusting for age, race, and MAP, after further adjusting for BMI, pack-years of smoking, diabetes, and medication for hypertension, and after additionally adjusting for lipids and medication for hyperlipidemia (Models I to III in the upper panel of Table 2).

Analyses using a log-transformed aortic calcium score show the similar results (Table 3). cfPWV had significant positive associations with log-transformed aortic calcium score in a crude analysis (Crude in Table 3) as well as after adjusting for age, race, and MAP (Model I in Table 3), after further adjusting for BMI, pack-years of smoking, diabetes, and medication for hypertension (Model II in Table 3), and after additionally adjusting for lipids and medication for hyperlipidemia (Model III in Table 3).

Race specific analyses show that cfPWV had a positive association with the category of aortic calcium score in each race (Table 4). The patterns of association of aortic calcification category with cfPWV were similar across races. No statistically significant interaction between race and categories of aortic calcium score in predicting cfPWV was observed (data not shown). We did not show the results of multiple regression analyses separately by race because race specific analyses violated an assumption of multiple regression analyses (homogeneity of variance).

Discussion

The present study has shown that aortic stiffness measured as cfPWV has a significant positive association with aortic calcification measured as aortic calcium score in population-based samples of middle-aged men, that the significant association remains after adjusting for age, MAP, BMI, pack-years of smoking, diabetes, and other factors, and that the significant association is observed both in categorical and continuous data analyses. The study has also shown the positive association across Black, Japanese, and White Americans as well as Koreans. This is the first study showing the significant association of aortic stiffness with aortic calcification in multi-ethnic population-based samples. The results suggest that aortic calcification is one mechanism responsible for aortic stiffness in middle-aged men.

The results of the current study might suggest that aortic calcification contributes to aortic stiffness in men as early as their 40's. cfPWV rises with age from 20's to 90's.⁴ The mean age of the participants of the current study was 45 whereas that in previous studies showing the significant positive association of cfPWV with aortic calcification are 66 among 193 healthy volunteers¹² and 58 among 900 women.¹³

Our finding of the significant positive association of cfPWV with aortic calcification is biologically plausible. Aortic calcification represents medial calcification or a combination of medial and intimal calcification whereas coronary calcification represents primarily atherosclerotic intimal calcification.^{20, 21} Medial calcification is believed to directly increase arterial stiffness. The media of the large arteries including the aorta is mainly composed of elastin, collagen, and vascular smooth muscle cells. Degeneration and fragmentation of elastin as well as overproduction of abnormal collagen contribute to arterial stiffness.¹ Fragmented elastic fibers are prone to calcification.²¹ Additionally, experimentally induced calcification in the medial fibers of the aorta in rats shows that increase in medial calcification increases aortic stiffness.⁸

We observed that aortic calcification was significantly associated with age, MAP, pack-years of smoking, and diabetes but not with LDL-C or HDL-C. A recent review by Jayalath et al. reported that clinical determinants of aortic calcification were age, hypertension, cigarette smoking, diabetes, and other factors.²² They also reported that the association of aortic calcification with LDL-C and HDL-C was inconsistent: five studies reported a significant correlation and the other five studies reported no correlation. More recently two population studies reported the association of CVD risk factors with aortic calcification. The Amish Family Calcification Study showed that aortic calcification had significant associations with age, LDL-C but not with BP or smoking status.²³ The Multi-Ethnic Study of Atherosclerosis showed that aortic calcification had significant associations with age, BP, pack-years of smoking, LDL-C and HDL-C but not with diabetes.²⁴ Inconsistent results are partly due to the difference in imaging methods, e.g., X-ray versus CT, the difference in assessing aortic calcification, e.g., abdominal aorta, thoracic aorta, versus entire aorta, and the difference in age and sex groups.

We used 100 and 400 for the cutoff points of aortic calcium score. Clinically meaningful cutoff points of calcium score of 100, 300, 400, and 1,000 are reported for coronary calcium score,^{25–27} but no such cutoff points are reported for aortic calcium score although some investigators used a cutoff point of 300.²⁸ We analyzed the data using quintiles among those with aortic calcium score > zero and the results did not change materially (data not shown).

If aortic calcification is causally linked to aortic stiffness, elucidating the biology of aortic calcification may reveal targets to prevent aortic stiffness. Currently investigated pharmacological interventions to improve aortic stiffness include anti-hypertensive

medication such as angiotensin-converting enzyme inhibitors, statins, and cross-link breakers.² In the future, pharmacological interventions targeting anti-vascular calcification may improve aortic stiffness. Vascular calcification is an actively regulated process similar to bone formation.²⁰ Currently bisphosphonates, calcimimetics, the phosphate binder lanthanum carbonate, and other agents are under investigation for their potential anti-vascular-calcification effects.²⁹

Limitations of the study

Several limitations of the study warrant discussion. The study was cross sectional in design and we cannot establish causality. The participants of the study were only men aged 40–49 and the results may not be generalizable to women or other age groups. The study had missing cases by 11% which might cause bias. We believe, however, that we would have observed a stronger association of cfPWV with aortic calcification if we could have examined all these subjects with missing data. This is because many of these subjects with missing data had obesity which did not allow us to record correct waveforms and because obesity has positive associations with both cfPWV and aortic calcification.³⁰ Although previous studies among healthy volunteers¹² and patients with hemodialysis⁹ show that abdominal aortic calcification as compared to thoracic aortic calcification had stronger association with PWV, the current study did not distinguish abdominal from thoracic aortic calcification.

The results of the current study have demonstrated a significant positive association of aortic calcification with its stiffness from multi-ethnic cohorts of men aged 40–49. The association is independent of BP, BMI, and other risk factors of cardiovascular disease. Clinically aortic calcification has been paid less attention as compared to coronary calcification.²⁵ Considering that aortic stiffness is an independent risk factor for CVD and all-cause mortality, further basic, clinical, and population research on aortic calcification is of critical importance.

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***Highlights**

- Aortic stiffness is an independent risk factor of cardiovascular disease.
- We examined the association of aortic stiffness with aortic calcification.
- We examined it in a population-based multi-ethnic cohort of 906 healthy men.
- Aortic stiffness was measured as carotid-femoral pulse wave velocity (cfPWV).
- cfPWV had a significant positive association with aortic calcification.

Figure.

Mean and standard deviation of cfPWV by the category of aortic calcium score

ACS: aortic calcium score

cfPWV: carotid-femoral pulse wave velocity

Table 1

Basic characteristics of Study participants by category of aortic calcium score in 2002 to 2006

	All (n=906)	ACS =0 (n=303)	ACS 1–100 (n=411)	ACS 101–400 (n=110)	ACS 400+ (n=82)	P for trend
Age (years)	45.2 (2.9)	45.0 (2.9)	45.2 (2.9)	45.7 (2.7)	46.0 (2.7)	0.002
Race (%)						
Blacks	8.9	9.9	8.3	9.1	8.5	
JA	30.5	35.3	26.3	29.1	35.4	
Koreans	32.1	27.7	33.1	39.1	34.1	
Whites	28.5	27.1	32.4	22.7	22.0	0.072
BP sys (mmHg)	123.8 (13.4)	121.4 (12.1)	124.2 (13.5)	126.8 (15.4)	126.6 (12.9)	<0.001
BP dia (mmHg)	75.2 (10.2)	73.1 (9.4)	76.1 (9.9)	77.9 (11.7)	77.2 (10.9)	<0.001
MAP (mmHg)	91.6 (10.8)	89.2 (9.8)	92.1 (10.6)	94.2 (12.5)	93.7 (11.1)	<0.001
Heart rate (/min)	65.8 (9.5)	65.0 (9.5)	66.1 (9.5)	66.6 (8.8)	66.3 (10.5)	0.263
BMI (kg/m ²)	27.0 (3.9)	25.2 (3.3)	27.5 (3.9)	27.4 (4.5)	27.0 (3.8)	<0.001
Smoking status						
Current (%)	20.6	17.2	15.8	30.0	45.1	
Former (%)	25.9	23.1	25.8	30.9	30.5	
Never (%)	53.4	59.7	58.4	39.1	24.4	<0.001
Pack year	7.3 (11.6)	5.3 (9.8)	6.3 (11.2)	10.9 (12.1)	15.0 (14.5)	<0.001
Drinker (%)	42.2	44.6	38.7	40.9	52.4	0.540
LDL-C (mg/dL)	124.3 (34.1)	122.6 (35.4)	126.7 (34.3)	119.1 (29.4)	124.8 (33.1)	0.710
HDL-C (mg/dL)	48.6 (13.0)	51.7 (13.3)	46.5 (11.7)	47.3 (13.0)	51.8 (15.5)	0.582
TG (mg/dL)	161.6 (115.8)	142.4 (104.7)	166.4 (108.3)	177.2 (142.0)	187.8 (141.6)	0.001
Diabetes (%)	8.4	5.6	7.5	17.3	11.0	0.003
Medication						
BP (%)	11.0	7.9	10.7	17.3	15.9	0.005
Lipid (%)	10.8	9.2	9.2	17.3	15.9	0.017

Values are expressed as mean (standard deviation).

ACS: aortic calcium score, JA: Japanese Americans, BP: blood pressure, MAP: mean arterial pressure, BMI: body-mass index, TG: triglycerides

Table 2

Association of cFPWV with aortic calcium score (categorical analysis)

	ACS =0 (n=303)	ACS 1–100 (n=411)	ACS 101–400 (n=110)	ACS 400+ (n=82)	P for trend
Model I	836 (10)	850 (9)	877 (17)	941 (19)	<0.001
Model II	848 (8)	841 (8)	870 (16)	944 (19)	<0.001
Model III	849 (10)	840 (8)	869 (16)	947 (19)	<0.001

Model I: adjusted for age, race, and mean arterial pressure

Model II: further adjusted for BMI, pack years of smoking, diabetes and medication for hypertension

Model III: further adjusted for LDL-C, HDL-C, triglycerides and medication for hyperlipidemia

cFPWV: carotid-femoral pulse wave velocity. For other abbreviations, see footnote in table 1.

Table 3

Association of cfPWV with aortic calcium score among those with aortic calcium score >zero (multiple linear regression analysis) (n=603)

	Standardized coefficient	P
Crude	0.116	0.004
Model I	0.104	0.006
Model II	0.102	0.008
Model III	0.107	0.006

Model I: adjusted for age, race, and mean arterial pressure

Model II: further adjusted for BMI, pack years of smoking, diabetes and medication for hypertension

Model III: further adjusted for LDL-C, HDL-C, triglycerides and medication for hyperlipidemia

cfPWV: carotid-femoral pulse wave velocity. For other abbreviations, see footnote in table 1.

Table 4

Race-specific association of cFPWV with aortic calcium score

	ACS =0 (n=30)	ACS 1–100 (n=34)	ACS 101–400 (n=10)	ACS 400+ (n=7)	P for trend
(A) Blacks					
Crude	796 (34)	855 (32)	903 (59)	1079 (70)	<0.001
Model I	812 (31)	850 (29)	907 (53)	1032 (65)	0.002
Model II	813 (33)	842 (31)	917 (56)	1055 (66)	0.001
Model III	815 (33)	835 (31)	912 (56)	1079 (69)	0.001
(B) Japanese Americans					
Crude	853 (20)	909 (19)	982 (36)	966 (38)	0.002
Model I	869 (19)	899 (19)	971 (34)	958 (36)	0.009
Model II	885 (19)	882 (18)	977 (34)	958 (36)	0.019
Model III	882 (19)	882 (19)	977 (34)	966 (38)	0.013
(C) Koreans					
Crude	790 (14)	807 (11)	800 (19)	913 (24)	<0.001
Model I	804 (13)	806 (10)	782 (18)	901 (22)	0.001
Model II	808 (13)	806 (10)	778 (18)	900 (23)	0.003
Model III	807 (13)	806 (10)	778 (18)	903 (23)	0.001
(D) Whites					
Crude	825 (23)	856 (18)	919 (41)	944 (48)	0.012
Model I	836 (22)	852 (17)	902 (40)	944 (46)	0.021
Model II	851 (22)	842 (17)	893 (40)	961 (48)	0.025
Model III	855 (23)	840 (17)	892 (40)	957 (48)	0.036

Model I: adjusted for age and mean arterial pressure

Model II: further adjusted for BMI, pack years of smoking, diabetes and medication for hypertension

Model III: further adjusted for LDL-C, HDL-C, triglycerides and medication for hyperlipidemia

cFPWV: carotid-femoral pulse wave velocity. For other abbreviations, see footnote in table 1.