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BRACHIAL-ANKLE PULSE WAVE VELOCITY IS ASSOCIATED WITH CORONARY CALCIFICATION AMONG 1,131 HEALTHY MIDDLE-AGED MEN

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Abstract

Background—Brachial-ankle pulse wave velocity (*baPWV*) is a simple and reproducible measure of arterial stiffness and is extensively used to assess cardiovascular disease (CVD) risk in eastern Asia. We examined whether *baPWV* is associated with coronary atherosclerosis in an international study of healthy middle-aged men.

Methods—A population-based sample of 1,131 men aged 40–49 years was recruited— 257 Whites and 75 Blacks in Pittsburgh, US, 228 Japanese-Americans in Honolulu, US, 292 Japanese

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*This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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in Otsu, Japan, and 279 Koreans in Ansan, Korea. *baPWV* was measured with an automated waveform analyzer (VP2000, Omron) and atherosclerosis was examined as coronary artery calcification (CAC) by computed-tomography (GE-Imatron EBT scanner). Association of the presence of CAC (defined as ≥ 10 Agatston unit) was examined with continuous measure as well as with increasing quartiles of *baPWV*.

Results—As compared to the lowest quartile of *baPWV*, the multivariable-adjusted odds ratio (95% confidence-interval [CI]) for presence of CAC in the combined sample was 1.70 (0.98, 2.94) for 2nd quartile, 1.88 (1.08, 3.28) for 3rd quartile, and 2.16 (1.19, 3.94) for 4th quartile (p -trend = 0.01). The odds for CAC increased by 19% per 100 cm/s increase ($p < 0.01$), or by 36% per standard-deviation increase ($p < 0.01$) in *baPWV*. Similar effect-sizes were observed in individual races, and were significant among Whites, Blacks and Koreans.

Conclusion—*baPWV* is cross-sectionally associated with CAC among healthy middle-aged men. The association was significant in Whites and Blacks in the US, and among Koreans. Longitudinal studies are needed to determine its CVD predictive ability.

Keywords

Vascular stiffness; atherosclerosis; vascular calcification; pulse wave analysis; arteriosclerosis

1.0 Introduction

Coronary heart disease (CHD) remains the leading cause of mortality in the United States (US) in spite of a significant decline in age-adjusted CHD over the past 5 decades.¹ The burden of CHD is expected to increase by 16% over the next 20 years due to an aging population and increased survival after suffering from a coronary event.² One of the current strategies for further reducing CHD is to implement prevention strategies among individuals who are at an intermediate CHD risk and who would benefit most from CHD prevention therapy.³

Coronary artery calcification (CAC), assessed by computed-tomography scan (CT), is a strong independent predictor of future CHD events among asymptomatic individuals. Use of CAC imaging is currently recommended among individuals who are at low to intermediate risk i.e. 10-year risk of cardiovascular disease (CVD) risk between 6%–20%.⁴ However, CAC imaging exposes an individual to ionizing radiation, which may limit its wider applicability as a screening tool. Also, the cost-effectiveness of routine CT imaging among asymptomatic individuals is not yet established.⁵

Brachial-ankle pulse wave velocity (*baPWV*) is a highly reproducible measure of arterial stiffness that has shown promise as a predictor of future CVD among east Asian populations.⁶ Unlike carotid-femoral pulse wave velocity (*cfPWV*), which is a measure of central arterial stiffness, *baPWV* is a combined measure of central and peripheral arterial stiffness.⁷ Although *cfPWV* is considered a gold standard marker for central arterial stiffness and a predictor of future CHD, it has not gained acceptance into clinical practice esp. in the West⁸ – possibly due to requisite operator training and expertise, and also patient's discomfort with groin exposure. In contrast, *baPWV* is currently used routinely in Japan and South Korea to assess CVD risk.⁹ *baPWV* requires application of cuffs on the four

extremities, is convenient to measure in a clinic, requires little technical expertise, and, unlike *cfPWV*, does not require exposure to the inguinal region. We have previously reported a significant association between *baPWV* and the presence of CAC among obese post-menopausal women in the US.¹⁰ However, the utility of *baPWV* in the US remains to be thoroughly examined.^{11,12}

We, therefore, examined the association between *baPWV* and presence of CAC in the Electron-beam computed tomography and Risk factor Assessment among Japanese and U.S. Men in the Post-World War II birth cohort (ERA JUMP Study), an international study of subclinical atherosclerosis among 40–49 year old men. We hypothesized that *baPWV* is significantly associated with presence of CAC in this healthy sample of middle-aged men.

2.0 Methods and Materials

2.1 Participants

During 2002–2006, a population-based sample of 1,335 men aged 40–49 years, with no clinical CVD or other severe diseases, was obtained from 4 centers: 310 Whites and 107 Blacks from Pittsburgh, Pennsylvania, US; 303 Japanese Americans from Honolulu, Hawaii, US; 313 Japanese from Kusatsu city, Shiga, Japan; and 302 Koreans from Ansan, Gyeonggi-do, South Korea as previously described.¹³ Written informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of the following institutions: the University of Pittsburgh, Pittsburgh, Pennsylvania, US; the Kuakini Medical Center, Honolulu, Hawaii, US; Shiga University of Medical Science, Otsu, Japan; and Korea University, Seoul, South Korea.

2.2 Pulse Wave Velocity Assessment

At the start of the study, staff from the University of Pittsburgh's Ultrasound Research Laboratory visited the Honolulu site to train the sonographers in Honolulu and from South Korea for PWV measurements. In addition, continuous quality control measures were implemented for all the sites, including Japan. PWV measurements were automatically generated using a noninvasive and automated waveform analyzer (VP2000, Omron, Japan). This device provides automated measures of *baPWV* on both right and left sides – average of the two sides was used for our study. Following 10 min of rest in a supine position, occlusion and monitoring cuffs were placed around both arms and both ankles of the participant. The arm cuffs were placed on the skin or over light clothing, and the ankle cuffs were directly placed over the skin. ECG electrodes were placed on both wrists and a phonocardiogram i.e. a microphone for detecting heart sounds was placed on the left edge of the sternum. The path length for *baPWV* was calculated using height-based formulae.¹⁴ PWV was calculated as the distance between arterial sites divided by the time between the feet of the respective waveforms. Intra-class correlations (ICC) for re-examination of *baPWV* was 0.97 within technician, and 0.91 between technicians.¹⁵

2.3 Coronary Artery Calcification

CAC scanning was performed with a GE-Imatron C150 EBT scanner (GE Medical Systems, South San Francisco, California) at all centers as published earlier in detail.¹⁶ Briefly, a

standardized protocol was used to perform CAC scanning; 30–40 contiguous, 3-mm-thick transverse images from the level of the aortic root to the apex of the heart were obtained during maximal breath holding by using electrocardiogram triggering (60 percent of the R-R interval) so that each 100 millisecond exposure was obtained during the same phase of the cardiac cycle.¹⁶ One trained reader at the University of Pittsburgh read the images using a DICOM (Digital Imaging and Communications in Medicine) workstation and software by AccuImage (AccuImage Diagnostic Corporation, San Francisco, California). The software program implements the widely accepted Agatston scoring method.¹⁷ The reader was blinded to the participant's characteristics and the study centers. ICC for re-examination of electron-beam computed tomography scans was 0.98. Presence of CAC was defined as ≥ 10 Agatston Unit (AU) as a score between 0–10 is likely to be noise;¹⁶ a cut-off value of 10 AU maximizes the positive predictive value of CAC for underlying plaque disease by minimizing any contribution from beam hardening or motion artifact.

2.4 Risk Factor Assessment

All participants underwent a physical examination, completed a lifestyle questionnaire, and a laboratory assessment as described previously.^{13,18,19} Body weight and height were measured while the participant was wearing light clothing without shoes. Body-mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure and heart rate were measured after the participant emptied his bladder and sat quietly for 5 minutes. Blood pressure was measured twice on right arm with an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan) using an appropriate sized cuff; average of the two measurements was used. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or use of anti-hypertensive medications.²⁰ Mean blood pressure (MBP) was calculated as: $[DBP + 1/3 \times (SBP - DBP)]$. Venipuncture was performed early in the clinic visit after a 12-hour fast. Blood samples were stored at -80°C and shipped on dry ice from all centers to the University of Pittsburgh. Serum lipids were determined using the protocol standardized by the Centers for Disease Control and Prevention.²¹ Serum glucose was determined by using hexokinase–glucose-6-phosphate-dehydrogenase enzymatic assay. Diabetes was defined as individuals with fasting glucose ≥ 7.0 mmol/l or use of medications for diabetes.²² Alcohol drinking was defined as drinking two or more times per week. Smoking was measured as history of ever smoking. Use of blood pressure-lowering, diabetes, and lipid-lowering medications were ascertained through questionnaire. Data collection procedures were standardized across all centers.

We excluded participants taking antihypertensive medications ($n=140$), those with extreme outliers i.e. CAC $>1,000$ AU ($n=3$), and those with extremely high *baPWV* i.e. *baPWV* $>2,000$ cm/s ($n=4$). The final sample for this study consisted of 1,131 men (257 Whites, 75 Blacks, 228 Japanese Americans, 292 Japanese in Japan, and 279 Koreans) with complete data.

2.5 Statistical Methods

Descriptive characteristics of the sample population were examined, including demographics, CVD risk factors, *baPWV*, and CAC. Comparisons of population

characteristics were made using t-tests for continuous variables, and chi-square tests for categorical variables. Non-parametric tests were used for skewed variables. Logistic regression was used to examine the association between *baPWV* (per 100 cm/s increase, per 1 SD increase) and presence of CAC (> 10 AU) – in an unadjusted model (crude model), in an age-, race-adjusted model (model I), as well as in multivariable models adjusted for CVD risk factors including race, age, SBP, LDL-c, ever smoking, and diabetes (model II), and further adjusting for HDL-c, BMI and alcohol drinking (model III). As the distribution of the CAC scores was skewed with a large majority of the participants having zero CAC score, tobit regression (PROC QLIM) with left-censored data was performed to examine the association of CAC with *baPWV*²³ – for this analysis, log-transformation was performed for non-zero CAC scores. Unadjusted analysis was also performed after stratification by race-ethnicity. Further, we categorized the *baPWV* into quartiles and examined their association with the presence of CAC keeping lowest quartile of *baPWV* as the reference category. Similar to the previous analysis, the association was examined using unadjusted model, race-adjusted, and multivariable-adjusted models in logistic regression; further unadjusted analyses was performed after stratification by race. All data analysis was performed using SAS/STAT software, version 9.3 of the SAS System, Cary, NC, USA.

3.0 Results

Participants with CAC ($n=191$) were slightly older (46.1 vs. 44.9 years, $p<0.001$), had higher BMI (27.0 vs. 25.4 kg/m², $p<0.001$), SBP (126.3 vs. 122.7 mmHg, $p<0.001$), LDL-c (3.5 vs. 3.3 mmol/l, $p<0.001$), and triglycerides (1.7 vs. 1.5 mmol/l, $p<0.01$) than those with no CAC ($n=940$). Prevalence of diabetes was non-significantly higher among those with CAC (8.4% vs. 5.6%, $p=ns$). Further, *baPWV* was significantly higher among those with CAC (1392.6 vs. 1317.0 cm/s among those with no CAC, $p<0.001$). (Table 1) The mean (SD) of *baPWV* (cm/s) among individual races was: Whites 1312.9 (150.8), Blacks 1370.0 (161.0), Japanese Americans 1415.3 (160.8), Japanese in Japan 1298.0 (174.8), and Koreans 1297.8 (137.2).

There was a trend for higher prevalence of CAC with higher *baPWV*. (Figure 1) With every 100 cm/s increase in *baPWV*, the odds for presence of CAC increased by 31% ($p<0.001$) in the crude model, 24% ($p<0.001$) after adjustment for age and race (model I), and 19% ($p<0.01$) in multivariable-adjusted models (model II and model III). Similarly, with every 1 SD increase in *baPWV*, the odds for CAC increased by 61% ($p<0.001$), 46% ($p<0.001$), and 36% ($p<0.01$) in crude, age-race adjusted and multivariable adjusted models respectively. (Table 2) When examining *baPWV* by quartiles, we found a significant trend for increasing prevalence of CAC with increasing *baPWV* quartiles in unadjusted and age-race adjusted models, as well as after multivariable-adjustment. (Figure 2) In a multivariable-adjusted tobit regression model, *baPWV* was significantly associated with higher CAC ($p=0.002$). In a supplementary analyses where we adjusted for MBP instead of SBP in the regression models, the results remained materially the same.

Among individual race-ethnicities, the prevalence of CAC was: Whites (24.9%), Blacks (15.7%), Japanese Americans (28.1%), Japanese in Japan (10.3%), and Koreans (10.0%). There was no significant interaction between race and *baPWV* in the model for the presence

of CAC ($p=0.28$). When analysis was performed after stratifying by race, in unadjusted model, the association between *baPWV* and CAC prevalence was significant among Whites (OR: 1.30 per 100 cm/s increase; $p<0.01$), Blacks (OR: 1.83 per 100 cm/s increase, $p<0.01$), and Koreans (OR: 1.36 per 100 cm/s increase; $p=0.03$); the association was not significant among Japanese Americans and Japanese in Japan although the odds for presence of CAC were higher with higher *baPWV*. (Table 2) When examining *baPWV* by quartiles in individual races, the analysis could not be performed among Blacks due to sample size limitations. Among other races, the p-trend for higher presence of CAC with higher quartiles of *baPWV* was significant among Whites in unadjusted models. (Supplementary table 1)

4.0 Discussion

We found that *baPWV* was significantly associated with CAC among healthy middle-aged men without CVD. This association was independent of traditional CVD risk factors. When stratified by race, the association was significant among Whites, Blacks, and Koreans. This is the first international study to examine the association between *baPWV* and coronary atherosclerosis among healthy middle-aged men.

Previous studies have reported a similar association of *baPWV* with CAC among 504 obese postmenopausal women in the US,¹⁰ and among 654 patients without CVD in Taiwan.²⁴ We have previously shown that among 504 obese postmenopausal women, the multivariable-adjusted odds ratio for presence of any CAC were 1.94 (95% CI 1.01, 3.70), 2.90 (95% CI 1.50, 5.58), and 2.21 (95% CI 1.11, 4.42) for quartiles 2, 3, and 4 respectively as compared to the lowest quartile of *baPWV*; the association was stronger for *baPWV* than for *cfPWV*.¹⁰ Similarly, in the Taiwanese study, the mean ($\pm$ SD) CAC score was higher (35.7 ± 173.6 , 100.2 ± 249.7 , and 227.6 ± 412.5 , $p\text{-trend}<0.001$) with higher *baPWV* (<1400 cm/s, 1400 cm/s- 1800 cm/s, and >1800 cm/s, respectively). Further, addition of *baPWV* to Framingham Risk Score (FRS) improved the area under curve (AUC) for prediction of CHD from 0.676 to 0.728.²⁴ Several clinical studies in eastern Asia have shown an association of *baPWV* with other intermediate CVD outcomes. For example, *baPWV* is reported to be positively associated with coronary stenosis in Korea,^{25–27} Japan,²⁸ Taiwan,²⁴ and China.²⁹ Our sample population was healthier than these studies i.e. our sample was younger and population-based. Additionally, the mean *baPWV* in our population was less than the *baPWV* reported from these studies. Examining this association among healthy men allowed us to assess the utility of *baPWV* as an early marker of CVD in an asymptomatic population.

baPWV measures arterial stiffness over the central and peripheral arterial tree. In contrast, *cfPWV* – a widely accepted marker of arterial stiffness – primarily measure stiffness in the central aortic trunk. A higher proportion of smooth muscle cells in the peripheral arteries, as compared to that in the aorta, may be one reason for higher velocity of transmission of the pulse wave in the peripheral vasculature. If true, this may at least partly explain the increased PWV observed in the measurement of *baPWV*, as compared to the *cfPWV*. However, given that aorta forms a large portion of the arterial tree over which *baPWV* is measured, 58% of the variation in *baPWV* can be explained by aortic PWV.³⁰ Further research is needed to examine pathogenesis of arterial stiffness especially in the peripheral muscular arteries.

Several factors may be responsible for the association between *baPWV* and coronary atherosclerosis as measured by CAC. Firstly, the pathogenesis of arterial stiffness possibly shares some common risk factors with atherosclerosis^{31,32} – this is more likely in the peripheral muscular arteries than in the central aortic trunk. We have previously shown that atherogenic lipoprotein particles are associated with *baPWV* and with femoral-ankle pulse wave velocity, but not with *cfPWV*.³³ In this regard, ankle-brachial index, an established measure of peripheral arterial disease, is also shown to be associated with coronary atherosclerosis.^{34,35} Secondly, arterial stiffness increases the mechanical stress on the arterial wall. This triggers molecular cascades that further triggers the growth of microvasculature within the vessel walls, and ultimately leads to microvasculature remodeling and damage.³⁶ These microscopic changes may be a fertile ground for the formation of atherosclerotic lesions. Finally, arterial stiffening reduces the cushioning effect of the aortic trunk that helps in maintaining coronary blood flow during the diastole. It increases cardiac afterload, thus increasing left-ventricular mass and requirement for coronary blood flow.³⁷

baPWV has a potential for wide clinical application. A recent meta-analysis has reported that *baPWV* is an independent predictor of total cardiovascular events, cardiovascular mortality, and all-cause mortality. However, 17 out of 18 studies used in this meta-analysis were conducted in eastern Asia.⁶ *baPWV* measurement is highly reproducible, much less expensive than CT, can be performed in a physician's office, requires little operator's expertise, and does not require exposure to the inguinal area. Currently, it is widely used in clinics in Japan and South Korea to assess the risk of future CVD. However, several concerns need to be addressed before it can be used as a clinical tool in the West, most important of which are (1) determination of normal reference values, and (2) applicability among Western populations.

Our results should be interpreted in light of the study limitations. As our data are cross-sectional, we cannot determine temporality of the association between *baPWV* and CAC; a scenario in which CAC leads to increase in *baPWV*, however, seems unreasonable. Our results are not generalizable to older populations or to women as our sample consisted of middle-aged men within a relatively narrow age range. However, use of this sample population allows us to examine our hypothesis in the age-group in which *baPWV* is most likely to be useful as an early screening tool. We defined presence of CAC as ≥ 10 AU as CAC score between 0 and 10 is likely to be noise.¹⁶ We had few participants with clinically significant CAC (i.e. CAC ≥ 400 AU) ($n=19$),³⁸ and thus, could not test association of *baPWV* with clinically significant CAC. Limited sample size within each race/ethnicity limited our ability to perform multivariable adjustment in a race-specific analysis.

5.0 Conclusion

In a population-based sample of healthy middle-aged men without CVD, *baPWV* is independently associated with coronary atherosclerosis measured by CAC. This association is consistent among Whites and Blacks in the US. Longitudinal studies to examine ability of *baPWV* to predict coronary atherosclerosis and CVD events in the Western populations are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Prevalence of CAC (10 - 99 AU and ≥ 100 AU) with *baPWV*

CAC = coronary artery calcification, AU = Agatston unit, *baPWV* = brachial-ankle pulse wave velocity

Figure 2. Association between *baPWV* and CAC: odds ratios for presence of CAC (≥ 10 AU) with increasing quartiles of *baPWV* (n=1,131)

Model I: Age, Race-adjusted.

Model II: Model I + systolic blood pressure, low-density lipoprotein cholesterol, ever smoking and diabetes

Model III: Model II + high-density lipoprotein cholesterol, alcohol drinking, heart rate and body-mass index

CAC = coronary artery calcification, AU = Agatston unit, *baPWV* = brachial-ankle pulse wave velocity

Table 1

Presence of cardiovascular risk factors among 40–49 year old men in the ERA JUMP Study, by presence of CAC (≥ 10 AU).

Population characteristic	CAC (n=191)	No CAC (n=940)	p-value
Age (years)	46.1 (2.6)	44.9 (2.9)	<0.001
BMI (kg/m ²)	27.0 (3.9)	25.4 (3.7)	<0.001
Systolic Blood Pressure (mmHg)	126.3 (12.9)	122.7 (13.3)	<0.001
Mean blood pressure (mmHg)	93.8 (9.9)	90.6 (10.9)	<0.001
Heart rate (per minute)	66.8 (9.5)	65.3 (0.0)	0.047
Hypertension (%) [§]	17.3	13.8	ns
Glucose (mmol/l)	5.8 (0.7)	5.8 (1.0)	ns
Diabetes (%) [‡]	8.4	5.6	ns
Pack-years of smoking [‡] , (years)	1.2 (0, 22)	2.5 (0, 19)	ns
Ever Smoking (%)	55.0	55.5	ns
Ethanol intake (g/day) [‡]	8.2 (0.4, 28.8)	7.5 (0.1, 24.7)	ns
Alcohol drinker (%)	49.7	47.3	ns
LDL-cholesterol (mmol/l)	3.5 (0.9)	3.3 (0.9)	<0.001
HDL-cholesterol (mmol/l)	1.3 (0.3)	1.3 (0.3)	ns
Triglycerides, (mmol/l) [‡]	1.7 (1.1, 2.3)	1.5 (1.0, 2.1)	0.04
baPWV (cm/s)	1392.6 (162.3)	1317.0 (160.8)	<0.001
CAC Score [‡]	45.5 (20.8, 99.9)	NA	
CAC Score ≥ 100 AU (%)	24.6	NA	

Values are mean ± SD unless otherwise mentioned.

[§] Hypertension was defined as presence of one or more of following – i) Systolic blood pressure (BP) ≥ 140 mmHg, ii) Diastolic BP ≥ 90 mmHg, or iii) use of antihypertensive medication

[‡] Diabetes was defined as either glucose ≥ 7 mmol/l or use of diabetic medication, or both

[‡] Median (IQR)

ns = not significant

CAC = Coronary Artery Calcification, AU = Agatston unit, LDL = low-density lipoprotein cholesterol, HDL = high-density lipoprotein cholesterol, baPWV = brachial-ankle pulse wave velocity, BMI = body-mass index, IQR = inter-quartile range

Table 2

Association between *baPWV* and CAC: odds ratio (95% confidence interval) for presence of CAC (≥ 10 AU) using continuous variables of *baPWV* (N=1,131)

	<i>baPWV</i> (per 100 cm/s)	<i>baPWV</i> (per SD change)	P-value
Crude	1.31 (1.20, 1.44)	1.61 (1.37, 1.90)	p<0.001
Model I	1.24 (1.12, 1.37)	1.46 (1.22, 1.74)	p<0.001
Model II	1.19 (1.06, 1.34)	1.36 (1.10, 1.67)	p=0.004
Model III	1.19 (1.05, 1.34)	1.36 (1.10, 1.68)	p=0.005
Race-Specific Analysis**			
Caucasian (n=281)	1.30 (1.07, 1.58)	1.49 (1.11, 2.01)	p=0.009
African American (n=83)	1.83 (1.22, 2.73)	3.03 (1.45, 6.33)	p=0.003
Japanese American (n=235)	1.17 (0.98, 1.40)	1.32 (0.97, 1.81)	p=0.078
Japanese in Japan (n=292)	1.15 (0.94, 1.41)	1.31 (0.88, 1.93)	p=0.183
Korean (n=280)	1.36 (1.03, 1.79)	1.55 (1.04, 2.31)	p=0.030

Model I: Age, Race-adjusted.

Model II: Model I + systolic blood pressure, low density lipoprotein-cholesterol, ever smoking, alcohol drinking, and diabetes

Model III: Model II + high density lipoprotein cholesterol, body-mass index and heart rate

CAC = coronary artery calcification, *baPWV* = brachial-ankle pulse wave velocity, AU = Agatston unit, SD = standard deviation

** Race-specific analysis was unadjusted for confounders