International Journal of Cardiology 189 (2015) 67–72

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Brachial-ankle pulse wave velocity is associated with coronary calcification among 1131 healthy middle-aged men ☆

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ARTICLE INFO

Article history:
Received 13 February 2015
Received in revised form 1 April 2015
Accepted 2 April 2015
Available online 3 April 2015

Keywords:
Vascular stiffness
Atherosclerosis
Vascular calcification
Pulse wave analysis
Arteriosclerosis

ABSTRACT

Background: Brachial-ankle pulse wave velocity (*ba*PWV) 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 *ba*PWV is associated with coronary atherosclerosis in an international study of healthy middle-aged men.

Methods: A population-based sample of 1131 men aged 40–49 years was recruited — 257 Whites and 75 Blacks in Pittsburgh, US, 228 Japanese-Americans in Honolulu, US, 292 Japanese in Otsu, Japan, and 279 Koreans in Ansan, Korea. *ba*PWV 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 *ba*PWV.

Results: As compared to the lowest quartile of *ba*PWV, the multivariable-adjusted odds ratio (95% Confidence Interval [CI]) for the 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 *ba*PWV. Similar effect-sizes were observed in individual races, and were significant among Whites, Blacks and Koreans.

Conclusion: *ba*PWV 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.

1. 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

☆ Funding Source: This work was supported by grants HL068200 and HL071561 from the National Institutes of Health, Bethesda, MD, USA, Korea Center for Disease Control and Prevention (Government budget code: 2004-E71001-00, 205-E71001-00) and grants B 16790335, A 13307016, 17209023, 21249043, A 25253046 and B 23390174 from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Tokyo, Japan).
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http://dx.doi.org/10.1016/j.ijcard.2015.04.020
0167-5273/

currently recommended among individuals who are at low to intermediate risk i.e. 10-year risk of cardiovascular disease (CVD) risk between 6% and 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 (*ba*PWV) 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 (*cf*PWV), which is a measure of central arterial stiffness, *ba*PWV is a combined measure of central and peripheral arterial stiffness [7]. Although *cf*PWV 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 West [8] — possibly due to requisite operator training and expertise, and also patient's discomfort with groin exposure. In contrast, *ba*PWV is currently used routinely in Japan and South Korea to assess CVD risk [9]. *ba*PWV requires application of cuffs on the four extremities, is convenient to measure in a clinic, requires little technical expertise, and, unlike *cf*PWV, does not require exposure to the inguinal region. We have previously reported a significant association between *ba*PWV and the presence of CAC among obese post-menopausal women in the US [10]. However, the utility of *ba*PWV in the US remains to be thoroughly examined [11,12].

We, therefore, examined the association between *ba*PWV and the 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 *ba*PWV is significantly associated with the presence of CAC in this healthy sample of middle-aged men.

2. Methods and materials

2.1. Participants

During 2002–2006, a population-based sample of 1335 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 *ba*PWV 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 *ba*PWV 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 *ba*PWV 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 the 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% 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 and 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 min. 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 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg or use of anti-hypertensive medications [20]. Mean blood pressure (MBP) was calculated as: $[DBP + 1/3 * (SBP - DBP)]$. 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 the 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 > 1000 AU ($n = 3$), and those with extremely high *ba*PWV i.e., *ba*PWV > 2000 cm/s ($n = 4$). The final sample for this study consisted of 1131 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, *ba*PWV, and CAC. Comparisons of population characteristics were made using t-tests for