Brachial-ankle pulse wave velocity is associated with coronary calcium in young and middle-aged asymptomatic adults: The Kangbuk Samsung Health Study

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A R T I C L E   I N F O

Article history: Received 16 March 2015
Received in revised form 4 May 2015
Accepted 21 May 2015
Available online 3 June 2015

Keywords: Arterial stiffness Pulse wave velocity Coronary artery calcium Atherosclerosis Subclinical disease

A B S T R A C T

Objective: To evaluate the association between brachial-ankle pulse wave velocity (baPWV), a convenient, non-radiating, readily available measurement of arterial stiffness, and coronary artery calcium (CAC), a reliable marker of coronary atherosclerosis, in a large sample of young and middle-aged asymptomatic adults; and to assess the incremental value of baPWV for detecting prevalent CAC beyond traditional risk factors.

Methods: Cross-sectional study of 15,185 asymptomatic Korean adults who voluntarily underwent a comprehensive health screening program including measurement of baPWV and CAC. BaPWV was measured using an oscillometric method with cuffs placed on both arms and ankles. CAC burden was assessed using a multi-detector CT scan and scored following Agatston’s method.

Results: The prevalence of CAC > 0 and CAC > 100 increased across baPWV quintiles. The multivariable-adjusted odds ratios (95% CI) for CAC > 0 comparing baPWV quintiles 2–5 versus quintile 1 were 1.06 (0.87–1.30), 1.24 (1.02–1.50), 1.39 (1.15–1.69) and 1.60 (1.31–1.96), respectively (P trend < 0.001). Similarly, the relative prevalence ratios for CAC > 100 were 1.30 (0.74–2.26), 1.59 (0.93–2.71), 1.74 (1.03–2.94) and 2.59 (1.54–4.36), respectively (P trend < 0.001). For CAC > 100, the area under the ROC curve for baPWV alone was 0.71 (0.68–0.74), and the addition of baPWV to traditional risk factors significantly improved the discrimination and calibration of models for detecting prevalent CAC > 0 and CAC > 100.

Conclusions: BaPWV was independently associated with the presence and severity of CAC in a large sample of young and middle-aged asymptomatic adults. BaPWV may be a valuable tool for identifying apparently low-risk individuals with increased burden of coronary atherosclerosis.

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.05.031
0021-9150/© 2015 Published by Elsevier Ireland Ltd.
1. Introduction

Cardiovascular disease (CVD) is a leading cause of mortality, disability and healthcare costs worldwide [1,2]. The extent of the CVD pandemic and its emergence in younger populations highlight the need for effective public health interventions focused on preventing and detecting CVD at its early stages.

Risk scores combining one-time measurements of traditional risk factors have a low sensitivity for identifying young adults at increased absolute cardiovascular risk [3,4]. Asymptomatic individuals with low score-based predicted risk but high burden of subclinical coronary atherosclerosis have increased CVD event rates and all-cause mortality [5,6]. However, until date no strategy for the identification of such individuals is recommended by clinical practice guidelines, which still rely on scores as the single first step for risk assessment [7,8].

Arterial wall stiffening is a complex process reflecting the combined effects of fragmentation of elastin fibers, collagen overproduction, smooth muscle necrosis of the arterial media, and calcium deposition [9]. Arterial stiffness is strongly related to aging, but it may be accelerated by cardiovascular risk factors such as hypertension or diabetes [10,11]. Thus, measurements of arterial stiffness may capture the exposure of arterial walls to cardiovascular risk factors over time. Brachial-ankle pulse wave velocity (baPWV) is a relatively simple, non-invasive, non-radiating and readily available combined measure of central and peripheral arterial stiffness, and is increasingly being used in Asian countries [12]. However, the role of baPWV in CVD risk assessment is uncertain [7,8]. Particularly, it is unclear whether baPWV can help identify subjects with subclinical coronary disease and therefore, at increased absolute risk [5,6].

The aim of our study was thus to assess the association between baPWV and coronary artery calcium (CAC), a powerful marker of coronary atherosclerosis and total plaque burden [13], in a large sample of apparently low-risk young and middle-aged asymptomatic adults, and to assess the incremental value of baPWV for detecting prevalent CAC beyond traditional risk factors.

2. Methods

2.1. Study subjects

The Kangbuk Samsung Health Study (KSHS) is a Korean cohort study based on all men and women 18 years of age or older who voluntarily undergo comprehensive health examinations at the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea. For the present cross-sectional analysis, we included all KSHS participants who had undergone cardiac CT scanning and baPWV measurement as part of their chosen comprehensive health exam from March 2010 until December 2013 (Fig. 1). In case a participant had more than one visit in which both baPWV and CAC had been measured, only the first visit was considered (N = 16,731). As the aim of our study was to assess the association between baPWV and CAC in stable, apparently healthy, young and middle-aged adults, we excluded 725 participants for one or more of the following criteria: age ≥70 years (N = 100), heart rate ≥120 beats per minute (N = 6), and history of cancer (N = 330), heart disease (defined as a self-reported history of angina, myocardial infarction, or arrhythmia that needed to be treated, N = 268), or stroke (N = 64). We further excluded 821 (5.1%) participants with missing data in any study variable. The final study sample included 15,185 participants (12,597 men and 2588 women).

The study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital. The requirement of informed consent was waived as the KSHS uses only de-identified data routinely collected during the health examinations.

2.2. Data collection

All examinations were conducted at the Kangbuk Samsung Health Screening Center clinics in Seoul and Suwon by trained personnel following a standardized protocol. A self-administered questionnaire was used to collect information on socio-demographic characteristics, lifestyle factors, medical history, family history and medication use. Height and weight were measured and the body mass index (BMI) was calculated as weight in kg divided by height in m squared. Trained nurses measured blood pressure in the sitting position at least three times using an automated oscillometric device. Blood was drawn from participants after fasting for ≥10 h and immediately sent to the Laboratory Medicine Department at the Kangbuk Samsung Hospital for testing. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Diabetes was defined as a self-reported history of diabetes, the use of glucose-lowering medications and/or HbA1c ≥6.5%. Family history of coronary heart disease and stroke were defined as a self-reported history of at least one first-degree relative with history of coronary heart disease or stroke, respectively.

BaPWV was measured in the supine position using a VP-1000 machine (OMRON, Japan) that recorded bilateral brachial and posterior tibial artery pressure waveforms using the oscilometric method with cuffs placed on both arms and ankles. BaPWV was calculated automatically for each arterial segment as the path length divided by the corresponding time interval. A validation study of baPWV measurements in an Asian population found that baPWV measurements had inter-observer and intra-observer correlation coefficients of 0.98 and 0.87, respectively [14]. The coefficients of variation in our sample for left and right baPWV were 12.3% and 12.6%, respectively. The average baPWV was calculated as the mean of the right and left measurements and used for the analyses.

Chest CT scans were obtained using a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan). All scans used the same standard scanning protocol of 2.5 mm slice thickness, 400 ms rotation time, 120 kV tube voltage, and ECG-gated dose modulated tube current of 124 mAS (310 mA*0.4 s). CAC was scored following Agatston's method [15]. CAC measurements had inter-observer and intra-observer intraclass correlation coefficients of 0.99 [16,17].

2.3. Statistical analysis

Demographic characteristics, cardiovascular risk factors and CAC burden of the study participants were calculated both overall and stratified by baPWV quintiles. Categorical variables are presented as number (%) and continuous variables as mean (SD) or median (IQR) based on the distribution of the data. Differences across quintiles were tested using chi-square tests, ANOVA or nonparametric tests. P values for linear trends across baPWV quintiles were calculated using logistic regression analysis.

Robust Tobit regression was used to assess the association between baPWV quintiles and ln(CAC + 1) with Huber-White estimation of standard errors. Log-transformations and Tobit regression were used because CAC scores are right skewed and left-censored at 0 [18]. Multivariable-adjusted CAC score ratios and 95% confidence intervals were calculated comparing quintiles 2–5 of baPWV to the lowest quintile. We also used logistic regression to model the presence of CAC > 0, and multinomial regression to
model CAC scores categorized as 0, 1–100 and > 100 with CAC = 0 as the base outcome. A CAC > 100 has been associated with high event rates, similar to secondary prevention populations [19]. In secondary analyses, we also modeled baPWV as a continuous variable (comparing the 90th vs the 10th baPWV percentiles), and also used restricted cubic splines for baPWV to obtain a detailed dose–response description of the association between baPWV and CAC.

For each regression analysis, we used three models to progressively adjust for potential confounders. We initially adjusted for age, gender, year of visit and study center (Model 1). Model 2 further adjusted for heart rate, systolic and diastolic blood pressure. In model 3, we further adjusted for BMI, pack-years of smoking, alcohol intake, physical activity, LDL cholesterol, HDL cholesterol, triglycerides, diabetes, EGFR, use of medications for hypertension and dyslipidemia, family history of heart disease and family history of stroke. The presence of peripheral artery disease may affect the accuracy of baPWV measurements. Thus, we repeated the analyses for left and right baPWV measurements separately. Additionally, we performed sensitivity analyses further adjusting for ankle-brachial index (ABI) measurements, and excluding participants with an ABI < 0.9 or > 1.3.

The area under the ROC curve (AUC) was calculated for both prevalent CAC > 0 and CAC > 100, for baPWV (alone) as a continuous variable. In addition, to test the incremental value of adding baPWV to a model including traditional cardiovascular risk factors for detecting prevalent CAC, we calculated performance measures comparing predicted probabilities for CAC > 0 and CAC > 100 derived from two models: model A (age, sex, total cholesterol, HDL cholesterol, current smoking, systolic blood pressure, hypertension medication use, and diabetes) versus model B (traditional risk factors plus baPWV). The improvement in discrimination with baPWV was evaluated by comparing the AUC and by using the net reclassification improvement (NRI) and the integrated discrimination index (IDI). The improvement in calibration with baPWV was evaluated using likelihood ratio tests and the Akaike information criterion (AIC).

A two-sided P value < 0.05 was considered significant. Statistical analyses were performed using Stata version 12 (StataCorp. 2011, College Station, TX).

3. Results

The mean age of the 15,185 study participants was 41.7 years and 83% were men. 25% were current smokers, 6% had diabetes, 9% used blood pressure-lowering medications and 5% lipid-lowering treatments (Table 1). Study participants in the highest baPWV quintiles were more likely to be older, male, current smokers, had higher BMI, blood pressure, total and LDL cholesterol, triglycerides and HbA1c, and had lower HDL cholesterol and EGFR.

Among study participants, 2142 (14%) had CAC > 0 and 354 (2%) had CAC > 100. CAC scores and the prevalence of CAC > 0 and CAC > 100 increased progressively across baPWV quintiles (all P trend < 0.001; Tables 2 and 3).

In fully-adjusted multivariable models, the CAC score ratios (95% confidence intervals) comparing quintiles 2–5 of baPWV to the lowest quintile were 1.21 (0.79–1.86), 1.51 (1.00–2.28), 2.10 (1.38–3.20), and 3.05 (1.98–4.70), respectively (P trend < 0.001; Table 2). In fully-adjusted restricted cubic spline models, the P values for non-linear spline terms were not statistically significant, indicating that the association of baPWV with ln(CAC + 1) was approximately linear. In these models, the CAC score ratio comparing participants in the 90th percentile to those in the 10th percentile of baPWV was 3.70 (95% CI 2.44–5.61).

Similarly, when CAC scores were categorized in two (CAC > 0 vs. CAC = 0) and three categories (0, 1–100 and > 100, CAC = 0 the...
reference) there was also a strong, progressive association between baPWV, the presence of any CAC (odds ratios for CAC > 0 comparing quintiles 2–5 of baPWV to the first quintile 1.06 [0.87–1.30], 1.24 [1.02–1.50], 1.39 [1.15–1.69] and 1.60 [1.31–1.96], respectively; P trend < 0.001), and the presence of CAC > 100 (relative prevalence ratios 1.30 [0.74–2.26], 1.59 [0.93–2.71], 1.74 [1.03–2.94] and 2.59 [1.54–4.36], respectively; P trend < 0.001) (Table 3 and Fig. 2). The results were similar when left and right baPWV measurements were used for the analyses instead of average baPWV. Sensitivity analyses further adjusting for ABI measurements or excluding participants with an abnormal ABI also yielded similar findings.

For CAC > 0, the AUC for baPWV (alone) was 0.65 (95% CI 0.64–0.66), and for CAC > 100 the AUC was 0.71 (95% CI 0.68–0.74). A threshold of baPWV > 13.5 m/s had a sensitivity for CAC > 100 of 70% and a specificity of 59% (60% correctly classified). Lower baPWV thresholds increased sensitivity but markedly reduced specificity. On the other hand, a threshold of >14.3 m/s had a specificity of 78% (sensitivity 51%, 77% correctly classified). The addition of baPWV to models including traditional risk factors significantly improved discrimination, with NRI s of 0.167 (P < 0.001) for CAC > 0 and 0.261 for CAC > 100 (P < 0.001) (Table 4). The improvement in the AUC and the IDI were also statistically significant (P < 0.001), even though the absolute improvement was only marginal. The addition of baPWV also improved the calibration of the models with significant likelihood ratio tests and lower AIC scores.

### 4. Discussion

In a large sample of young and middle-aged asymptomatic adults, baPWV was strongly and progressively associated with the presence and burden of CAC, a reliable marker of coronary atherosclerosis. This association remained significant after controlling for a wide range of traditional cardiovascular risk factors and other potential confounders. Moreover, baPWV improved the ability of standardized measurements of traditional risk factors for detecting prevalent CAC > 0 and CAC > 100. BaPWV may thus help identify young and middle-aged asymptomatic individuals with increased burden of subclinical coronary atherosclerosis.

While clinical CVD events occur in the second half of life, atherosclerosis and other vascular changes responsible for these events begin early in life [20]. As a consequence, preventive interventions may be more effective at young ages [21], before atherosclerosis lesions are complex and irreversible. Accordingly, preventive efforts should prioritize the identification and control of subclinical atherosclerosis in young and middle-aged subjects. Cardiovascular risk scores have shown a limited utility in this group [3,4], mainly as a result of the predominant effect of chronological age on risk estimation. In our study, despite a mean age of 41 years, 2% of the study participants had CAC > 100, a threshold that has been associated with high event rates [19]. Imaging or serum biomarkers such as CAC, high sensitivity C-reactive protein or carotid...
ultrasound imaging provide opportunities for further cardiovascular risk assessment. However, as tests involving radiation exposure (CACS), time for image acquisition and interpretation (carotid imaging) and healthcare costs, currently they are not recommended as CVD screening tools in American or European guidelines [7,8,22].

Table 3
Association of brachial-ankle pulse wave velocity and the presence of CAC > 0 and CAC > 100.

<table>
<thead>
<tr>
<th>Brachial-ankle pulse wave velocity</th>
<th>1st quintile</th>
<th>2nd quintile</th>
<th>3rd quintile</th>
<th>4th quintile</th>
<th>5th quintile</th>
<th>P value for trend</th>
<th>P90 versus P10</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC &gt; 0 AU (vs CAC = 0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>204 (6.8)</td>
<td>301 (9.9)</td>
<td>393 (12.9)</td>
<td>493 (16.2)</td>
<td>751 (24.7)</td>
<td>&lt;0.001</td>
<td>1.94 (1.72, 2.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1 (Reference)</td>
<td>1.11 (0.91, 1.35)</td>
<td>1.35 (1.12, 1.63)</td>
<td>1.58 (1.32, 1.90)</td>
<td>2.04 (1.71, 2.43)</td>
<td>&lt;0.001</td>
<td>1.70 (1.49, 1.95)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Model 2 (Reference)</td>
<td>1.07 (0.88, 1.30)</td>
<td>1.26 (1.05, 1.53)</td>
<td>1.43 (1.19, 1.73)</td>
<td>1.71 (1.41, 2.07)</td>
<td>&lt;0.001</td>
<td>1.60 (1.39, 1.83)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Model 3 (Reference)</td>
<td>1.06 (0.87, 1.30)</td>
<td>1.24 (1.02, 1.50)</td>
<td>1.39 (1.15, 1.69)</td>
<td>1.60 (1.31, 1.96)</td>
<td>&lt;0.001</td>
<td>1.56 (1.39, 1.83)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Model 1 adjusted for year of visit, study center, age and sex.
Model 2 further adjusted for systolic blood pressure, diastolic blood pressure and heart rate.
Model 3 further adjusted for BMI, pack-years of smoking, alcohol intake, physical activity, LDL cholesterol, HDL cholesterol, triglycerides, diabetes, EGFR, medication use for hypertension, medication use for dyslipidemia, family history of heart disease and family history of stroke.

Arterial stiffening is strongly related to aging. However, cardiovascular risk factors such as hypertension or diabetes can accelerate the process [10,11]. Accordingly, measurements of arterial stiffness such as baPWV may capture the exposure of arterial walls to these risk factors over time. In our study, subjects with higher baPWV were older and had a worse CVD risk profile. BaPWV measurements were robustly and strongly associated with the presence and burden of CAC. This is biologically plausible as both atherosclerosis and arterial stiffening share some risk factors. Furthermore, baPWV improved the ability of traditional risk factors (measured using standardized procedures and validated questionnaires) for detecting prevalent CAC. This information may help decide when to order a CAC scan, and aid in the interpretation of the score [23].

The association between baPWV and CAC was significant after adjusting for a wide range of potential confounders measured following standardized procedures. Central arterial stiffness results in increased systolic blood pressure, pulse pressure, and left ventricle afterload, with subsequent myocardial hypertrophy, increased oxygen demands, and reduced diastolic coronary perfusion [24,25]. Beyond triggering acute coronary events, these mechanisms may result in the progression of atherosclerosis [26].
Furthermore, altered mechanical properties of the vessel wall may play a role in the development of atherosclerosis [27]. On the other hand, it has also been suggested that atherosclerosis, through endothelial cell dysfunction and changes in the vascular wall, may result in increased vascular stiffness [27]. Experimental models and prospective studies are needed to better understand the mechanisms involved in this independent association, their temporal sequence, and the factors determining individual susceptibility to each process.

Our findings are consistent with those from previous studies on the association between measures of arterial stiffness and CAC. Nevertheless, previous studies on the association between baPWV and CAC used smaller samples, restrictive inclusion criteria and/or adjusted for a limited set of potential confounders, and did not conduct a detailed analysis of the dose–response association [12,28–30]. Similarly, studies assessing the independent association between alternative measurements of arterial stiffness such as carotid-femoral PWV and CAC focused on older, higher-risk populations [31–33]. A previous study on the association between baPWV and CAC in a smaller sample of non-hypertensive, non-diabetic screenees in the Kangbuk Samsung Hospital used restrictive inclusion criteria and adjusted only for a limited set of confounders, and did not present detailed dose–response data [34]. Our study thus provides a detailed description of the independent, progressive association between baPWV, a convenient measure of arterial stiffness, and CAC, in a very large sample of young and middle-aged, asymptomatic, apparently healthy men and women. BaPWV has been shown to predict CVD events and all-cause mortality [35], and the addition of baPWV to the Framingham and SCORE equations improved the prediction of incident CVD events beyond traditional risk factors [36,37]. Nevertheless, the added value of baPWV for detecting the presence of subclinical disease in young and middle-aged asymptomatic adults had not yet been tested.

From a clinical perspective, baPWV, a convenient, non-radiating, relatively inexpensive and readily available tool, may help identify asymptomatic apparently low-risk subjects at increased risk of prevalent subclinical coronary atherosclerosis. These subjects may benefit from more aggressive lifestyle interventions, closer follow-up, early re-assessment, or additional testing. Further research is still needed to better understand the potential role of baPWV as a screening/risk assessment tool, including population-based studies to define age, race/ethnicity and sex reference values and baPWV cutoffs, prospective studies with clinical outcomes, and cost-effectiveness studies.

Our findings must be interpreted in the context of some limitations. First, the cross-sectional nature of our study precludes causal inference. Second, arterial stiffness was measured using baPWV. Even though carotid-femoral PWV is considered the gold standard measurement of arterial stiffness in European countries [38], baPWV is widely used in Asia, and studies have shown a high correlation between baPWV and measurements of central arterial stiffness [39]. Moreover, because of its simplicity, baPWV may be a more convenient tool for assessing arterial stiffness in clinical settings. Finally, our study population was comprised of Korean adults voluntarily attending health screening exams. Therefore, the generalizability of these results to other populations is unknown.

Our study has several strengths. The study population was relatively young, thus less likely to be affected by co-morbidities, use of medications, and selection bias than older populations. The large sample size and the availability of high-quality data subject to the careful standardization and quality control in the KSHS reduced measurement error and added to the strength of the findings.

5. Conclusion

We found a strong, independent association between baPWV, a measure of arterial stiffness, and CAC in a large population of young and middle-aged asymptomatic adults. Moreover, baPWV improved the detection of prevalent CAC when added to traditional risk factors. BaPWV may thus help identify asymptomatic young and middle-aged individuals with an increased burden of subclinical coronary atherosclerosis. Prospective multi-ethnic and cost-effectiveness studies will provide further insights on the value of baPWV in clinical practice.

Sources of funding

Miguel Cainzos-Achirica was funded by a research grant from the Spanish Society of Cardiology.

Conflict of interest

None.

References


