Original Article

Yonsei Med J 2017 Sep;58(5):954-958
https://doi.org/10.3349/ymj.2017.58.5.954

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Association of Inter-Arm Systolic Blood Pressure Difference with Coronary Atherosclerotic Disease Burden Using Calcium Scoring

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Purpose: There are no sufficient data on the correlation between inter-arm blood pressure (BP) difference and coronary atherosclerosis found using coronary artery calcium score (CACS). We aimed to investigate if the increased difference in inter-arm BP is independently associated with severity of CACS.

Materials and Methods: Patients who had ≥3 cardiovascular risk factors or an intermediate Framingham Risk Score (FRS; ≥10) were enrolled. Inter-arm BP difference was defined as the absolute difference in BP in both arms. Quantitative CACS was measured by using coronary computed tomography angiography with the scoring system.

Results: A total of 261 patients were included in this study. Age (r=0.256, p<0.001), serum creatinine (r=0.139, p=0.030), mean of right arm systolic BP (SBP; r=0.172, p=0.005), mean of left arm SBP (r=0.190, p=0.002), inter-arm SBP difference (r=0.152, p=0.014), and the FRS (r=0.278, p<0.001) showed significant correlation with CACS. The increased inter-arm SBP difference (≥6 mm Hg) was significantly associated with CACS ≥300 [odds ratio (OR) 2.17, 95% confidence interval (CI) 1.12–4.22; p=0.022]. In multivariable analysis, the inter-arm SBP difference ≥6 mm Hg was also significantly associated with CACS ≥300 after adjusting for clinical risk factors (OR 2.34, 95 % CI 1.06–5.19; p=0.036).

Conclusion: An increased inter-arm SBP difference (≥6 mm Hg) is associated with coronary atherosclerotic disease burden using CACS, and provides additional information for predicting severe coronary calcification, compared to models based on traditional risk factors.

Key Words: Inter-arm blood pressure, difference, coronary artery, calcium score, atherosclerosis

INTRODUCTION

Identification of patients with high risk for cardiovascular (CV) disease is important to justify more aggressive medical therapies for primary prevention.[1,2] The coronary artery calcium score (CACS) has been used to non-invasively evaluate CV risk.[3] CACS is correlated with coronary artery plaque burden, and previous studies have demonstrated a relationship between CACS and all-cause mortality independent of other established risk factors.[4,5] However, CACS requires radiation exposure, equipment, training, and time, and is poorly reimbursed, thus limiting their routine use in daily practice.

Recently, there has been growing interest in the difference in inter-arm blood pressure (BP), especially because increased differences in systolic BP (SBP), and also weakly in diastolic BP (DBP), are associated with a greater risk of CV events, and also both all-cause and CV mortality.[6-9] Recent studies have also identified a correlation between the difference in inter-arm BP and

Received: February 6, 2017 **Revised:** May 21, 2017
Accepted: May 22, 2017
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•The authors have no financial conflicts of interest.

target organ damage such as left ventricular mass index and carotid or brachial-femoral pulse wave velocities.[10,11] However, there are not much data on the relationship between the difference in inter-arm BP and coronary atherosclerotic disease, found by using CACS.

In the present study, therefore, we aimed to investigate whether the increased difference of inter-arm BP was independently associated with an abnormal CACS. Identification of an association between inter-arm BP difference and CACS may have significant implications for screening patients for atherosclerotic coronary artery disease (CAD).

MATERIALS AND METHODS

Study population

Included patients had at least 3 CV risk factors or an intermediate Framingham Risk Score (FRS; ≥10), were referred to the hospital with chest pain, and underwent evaluation of CAD between March 2012 and August 2014. A total of 261 patients who underwent coronary computed tomography angiography (CTA) at the discretion of their treating physician were included in the analysis. Patients with known CAD, a previous history of revascularization, peripheral artery disease, and those with significant valvular heart disease were excluded from the analysis. The study protocol was approved by the Institutional Review Board of Ulsan University Hospital, and is in accordance with the Declaration of Helsinki.

The presence of known CV risk factors, including smoking history, hypertension, diabetes mellitus, and dyslipidemia, were identified through history taking and using medical questionnaires. Smoking was classified as never, current, or ex-smoker, with smoking stopped less than 1 year before enrollment. Hypertension was diagnosed if patients had SBP ≥140 mm Hg or DBP ≥90 mm Hg, a history of hypertension or were using anti-hypertensive agents. Diabetes mellitus was diagnosed if patients had a fasting plasma glucose level ≥126 mg/dL on 2 separate days, a history of diabetes mellitus or were using anti-diabetic agents. Dyslipidemia was diagnosed in patients with a history of using cholesterol-lowering medications or who had a fasting serum total cholesterol level ≥240 mg/dL or low-density lipoprotein cholesterol level ≥160 mg/dL. The FRS was used to estimate a 10-year risk of coronary heart disease, defined as angina pectoris, recognized or unrecognized myocardial infarction, coronary insufficiency, and cardiac death.[12] The FRS score included age, gender, total cholesterol, high-density lipoprotein cholesterol, SBP, and use of anti-hypertensive agents as its individual components.

Measurement of blood pressure and inter-arm blood pressure difference

BP was synchronously measured in both arms by a trained nurse using separate cuff hoses in each electronic manometer (Omron HEM-7001-E; Omron Corp., Tokyo, Japan). The BP was measured 3 times at two-minute intervals in each patient on the day of the examination. Thus, the patients were instructed to sit for 5 minutes on a straight chair with BP cuffs wrapped around both arms before performing the BP measurements. Inter-arm BP difference was defined as right-arm BP minus left-arm BP. Then, the absolute value of the inter-arm BP difference was calculated.

Coronary artery calcium score using coronary computed tomography angiography

Coronary CTA was performed using a 0.8-mm thickness 256-slice multi-detector CT scanner (Brilliance iCT 256; Philips Medical Systems, Best, the Netherlands).[13] Patients with a heart rate >65 bpm were given metoprolol 100 mg to reduce their heart rate down to ≤65 bpm. Scan parameters were as follows: tube voltage, 120 kVp; tube current, 100 mAs; 220 mm field of view; rotation time, 0.27 s/rotation; reconstructed slice thickness, 0.8-mm; signal acquisition at 80 % of the R-R interval. CACS was measured using the Extended Brilliance Workspace workstation (Philips Medical Systems) after reconstruction. CACS was automatically displayed in color by calcium scoring software. Quantitative CACS was measured with the scoring system described by Agatston.[14] We excluded the patients with 0 of CACS.

Statistical analysis

Continuous variables are presented as mean±standard deviation, whereas categorical variables are expressed as absolute values and percentages. The Wilcoxon rank-sum test for independent samples was used to identify differences between continuous variables that were not normally distributed. Student's t-test was used to identify differences between normally distributed continuous variables. Differences between categorical variables were evaluated with the Fisher exact test. Bivariate correlation analysis with Spearman correlations was used to evaluate associations between variables. Multivariate logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the CACS and other variables. To evaluate whether inter-arm BP difference provides incremental value in predicting the CACS over traditional risk factors, we computed receiver operating characteristic (ROC) curves, and the DeLong method was then used to identify differences between ROC curves. All statistical analyses were done using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA), and $p<0.05$ was considered significant.

RESULTS

The demographic and clinical characteristics of patients are presented in Table 1. Included patients had a mean age of 60.6±9.1 years, and 150 patients (57.0 %) were male. The mean value of inter-arm BP difference for SBP/DBP was 5.4/3.3 mm Hg, the mean value of FRS was 10.2±7.3, and CACS was 169.4±326.6. Table 2 shows the correlations of various parameters with the degree of CACS: Age (r=0.256, *p*<0.001), serum creatinine (r=0.139, *p*=0.030), mean of right arm SBP (r=0.172, *p*=0.005), mean of left arm SBP (r=0.190, *p*=0.002), inter-arm SBP difference (r=0.152, *p*=0.014), and the FRS (r=0.278, *p*<0.001) showed a significant correlation with CACS.

As shown in Table 3, an inter-arm SBP difference ≥6 mm Hg was significantly associated with a CACS ≥300 (OR 2.17, 95% CI 1.12–4.22; *p*=0.022). This relationship was maintained even after adjustment for covariates including age ≥50 years, gender, hypertension, diabetes mellitus, dyslipidemia, body mass index, absolute inter-arm SBP difference, and FRS (OR 2.34, 95% CI 1.06–5.19; *p*=0.036). Additionally, the frequency of patients with increased inter-arm SBP difference was significantly different between patients stratified by CACS ≥300 (Table 4). Moreover, when the inter-arm SBP difference was added to a model that included the FRS, a significant improvement resulted in the ability to predict an abnormal CACS (≥300), shown in Fig. 1. Specifically, additional inclusion of inter-arm SBP difference to the FRS increased the area under the curve for predicting CACS ≥300, from 0.664 to 0.721 (*p*<0.0001).

Table 1. Baseline Clinical Characteristics

Variable	n=261
Age (yr)	60.6±9.1
Men, n (%)	150 (57.0)
BMI (kg/m^2)	24.4±3.0
Hypertension, n (%)	131 (50.2)
Diabetes mellitus, n (%)	61 (23.4)
Dyslipidemia, n (%)	140 (53.6)
Current smoker, n (%)	49 (18.8)
Laboratory findings	
Creatinine (mg/dL)	1.0±0.2
Total cholesterol (mg/dL)	190.8±41.1
Triglyceride (mg/dL)	141.5±84.3
HDL cholesterol (mg/dL)	49.3±11.8
LDL cholesterol (mg/dL)	112.8±35.4
hs-CRP (mg/L)	0.2±0.7
Ejection fraction (%)	65.4±5.5
SBP of right arm (mm Hg)	135.2±17.7
SBP of left arm (mm Hg)	132.4±16.9
DBP of right arm (mm Hg)	80.1±9.7
DBP of left arm (mm Hg)	79.3±9.4
Absolute inter-arm SBP difference (mm Hg)	5.4±4.1
Absolute inter-arm DBP difference (mm Hg)	3.3±2.2
FRS (% per 10 yr)	10.2±7.3
CACS	169.4±326.6

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; CACS, coronary artery calcium score.
Data are mean±SD or n (%).

DISCUSSION

The main findings in our study are; 1) increased inter-arm SBP

Table 2. Bivariate Analysis Showing Correlation between CACS and Various Parameters

Variable	r	*p* value
Age	0.256	<0.001
Creatinine	0.139	0.030
Total cholesterol	-0.102	0.108
LDL cholesterol	-0.089	0.189
hs-CRP	0.030	0.678
Ejection fraction	-0.084	0.193
Mean of right arm SBP	0.172	0.005
Mean of left arm SBP	0.190	0.002
Mean of right arm DBP	0.005	0.933
Mean of left arm DBP	0.022	0.726
Absolute inter-arm SBP difference	0.152	0.014
Absolute inter-arm DBP difference	0.085	0.196
FRS	0.278	<0.001

CACS, coronary artery calcium score; LDL, low-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score.

Table 3. Multivariate Logistic Regression Analysis Showing the Association between Degree of CACS (≥300) and Various Parameters

Variable	Unadjusted		Adjusted*	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.09 (1.05–1.13)	<0.001	1.10 (1.03–1.18)	0.005
Diabetes mellitus	1.50 (0.74–3.17)	0.247	1.30 (0.53–3.22)	0.567
Hypertension	1.47 (0.76–2.84)	0.256	1.13 (0.48–2.67)	0.788
Women	0.97 (0.50–1.88)	0.923	0.64 (0.19–2.17)	0.477
Dyslipidemia	1.57 (0.80–3.07)	0.190	1.42 (0.62–3.26)	0.410
BMI	0.96 (0.85–1.07)	0.434	1.05 (0.90–1.21)	0.556
Absolute inter-arm SBP difference ≥6 mm Hg	2.17 (1.12–4.22)	0.022	2.34 (1.06–5.19)	0.036
FRS ≥10	2.02 (1.04–3.91)	0.038	1.34 (0.44–4.12)	0.608

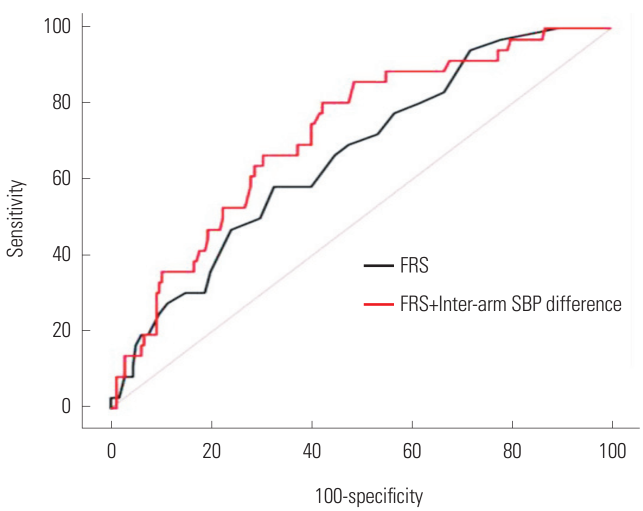
CACS, coronary artery calcium score; OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; FRS, Framingham Risk Score.
*ORs have been adjusted for age ≥50 years, gender, hypertension, diabetes mellitus, dyslipidemia, BMI, absolute inter-arm SBP difference ≥6 mm Hg, FRS ≥10.

https://doi.org/10.3349/ymj.2017.58.5.954

Table 4. Frequency of Patients with Increased Inter-Arm SBP Difference Stratified by CACS

CACS	Total (n=261)	Inter-arm SBP difference		*p* value
		(≥6 mm Hg, n=110)	(<6 mm Hg, n=151)	
1–99 (%)	170 (65.1)	65 (59.1)	105 (69.5)	0.080
100–299 (%)	48 (18.4)	20 (18.2)	28 (18.6)	0.941
≥300 (%)	43 (16.5)	25 (22.7)	18 (11.9)	0.020

CACS, coronary artery calcium score; SBP, systolic blood pressure.



	C-statistics	95% CI	*p* value
FRS	0.664	0.596–0.728	0.0005
FRS+Inter-arm SBP difference	0.721	0.655–0.781	<0.0001

Fig. 1. Comparison of the receiver operating characteristic curves for inter-arm SBP difference in addition to a model of the 10-year CHD risk (FRS) to predict an abnormal CACS (≥300). CACS, coronary artery calcium score; SBP, systolic blood pressure; FRS, Framingham Risk Score; CHD, coronary heart disease, CI, confidence interval.

difference (≥6 mm Hg) is an independent predictor for coronary atherosclerosis using CACS even after adjusting for known CV risk factors; 2) inter-arm SBP difference provides additional information for predicting severe coronary calcification compared to models based on known traditional risk factors.

Recently, a great deal of interest has been paid on the predictive value of inter-arm BP difference for clinical outcomes. Previous data have indicated that an increased difference in inter-arm SBP is associated with an increased risk of subclinical atherosclerosis, left ventricular hypertrophy, aortic aneurysms and aortic dissection, and CV disease.[9,10,15-17] In addition, a recent meta-analysis, based on 9 studies including over 15617 patients,[7] demonstrated that a greater difference in inter-arm SBP was a predictor of increased all-cause and CV mortality. However, there were some limitations to these previous studies. Most of the evidence on CV disease came from studies measuring BP sequentially in both arms, instead of synchronous measurements as in our study. Sequential BP measurements have been shown to overestimate the prevalence of an increased inter-arm BP difference.[18] Also, there are a lack of studies assessing the correlation between inter-arm BP difference and coronary atherosclerosis using CACS as measured by coronary CTA. In this regard, our data give more meaningful information for significant association of synchronously measured inter-arm BP difference with CACS obtained from coronary CTA in outpatient daily practice.

CACS has been shown to provide an increased predictive value over traditional CV disease risk factors. Indeed, CACS is a robust predictor of CV events and all-cause mortality for individuals with an intermediate CV risk.[4,19-21] Current guidelines give a Class IIa recommendation for the use of CACS in individuals at intermediate CV risk.[20,21] Moreover, a recent study suggested that an increasing CACS was significantly associated with a higher risk of all-cause mortality among patients with a very low CV risk factor profile.[22] In the present study, our data showed that inter-arm SBP difference was significantly correlated with the degree of CACS. When we focused our analysis on CACS ≥300, as this is known to identify those at the highest risk of CV events,[23] the cutoff value of inter-arm SBP difference ≥6 mm Hg was shown to be an independent predictor of CACS ≥300, especially in patients who had at least an intermediate risk of CV disease.

Although CACS is the most validated marker of coronary atherosclerosis among non-invasive imaging modalities, valid questions on radiation exposure and cost-effectiveness are major limitations to its repeated use in routine outpatient daily practice. In our study, additional inclusion of inter-arm SBP difference improved the ability of risk prediction models, which are based on traditional risk factors for coronary atherosclerosis such as FRS. In this regard, inter-arm SBP difference may be an alternative option for screening patients for coronary atherosclerosis.

The present study has several limitations. First, since our study had an observational study design, the identified associations do not necessarily confirm causation. Furthermore, due to the absence of randomization from the general population, generalization of our findings is restricted. However, because this study has important findings on the value of inter-arm SBP difference in patients who had at least an intermediate risk of CV disease, confirmation with larger randomized studies is needed. Second, we used multivariable analysis for FRS and incorporated known CAD risk factors such as age, hypertension, diabetes mellitus, and dyslipidemia that would be associated with inter-arm BP difference. However, we could not clearly adjust for other non-traditional risk factor for CAD. Finally, we enrolled those patients who had ≥3 CV risk factors or a predominantly intermediate FRS (FRS ≥10). Therefore, the application of our findings is limited to patients who had at least an intermediate risk of CV disease, and generalizability of our findings to patients with low risk of severe coronary calcification needs further confirmation.

In conclusion, an increased inter-arm SBP difference (≥6 mm Hg) is an independent predictor for coronary atherosclerosis using CACS and provides additional information for predicting severe coronary calcification, compared to models based on known traditional risk factors. Patients with evidence of increased inter-arm SBP difference may warrant a more thorough evaluation for coronary atherosclerotic disease with CACS.

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