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Original Article

Brachial-Ankle Pulse Wave Velocity is Associated with Composite Carotid and Coronary Atherosclerosis in a Middle-Aged Asymptomatic Population

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***Aim*: Although arterial stiffness has been associated with the development of atherosclerosis, the role of brachial-ankle pulse wave velocity (baPWV) for diagnosing composite coronary and carotid atherosclerosis has not been completely elucidated.**
***Method*: We enrolled 773 asymptomatic individuals who were referred from 25 public health centers in Seoul and who underwent carotid ultrasonography and coronary computed tomography. Non-invasive hemodynamic parameters, including baPWV, were also measured. Composite coronary and carotid atherosclerosis was defined as follows: 1) coronary artery calcium (CAC) score ≥ 100, 2) coronary artery stenosis (CAS) ≥ 50% of diameter stenosis, 3) carotid intima medial thickness (CIMT) ≥ 0.9 mm, or 4) presence of carotid artery plaque (CAP).**
***Results*: The incidence of composite coronary and carotid atherosclerosis was 28.2%. Coronary atherosclerosis (CAC and CAS) was significantly associated with carotid atherosclerosis (CIMT and CAP). Subjects with higher baPWV (highest quartile) had a higher prevalence of composite coronary and carotid atherosclerosis ($p<.001$). Although multivariate analysis failed to show baPWV as an independent predictor for composite atherosclerosis, baPWV had moderate diagnostic power to detect a subject with more than two positive subclinical atherosclerosis exams [area under the curve (AUC), 0.692].**
***Conclusion*: baPWV was associated with the composite coronary and carotid atherosclerotic burden in a community-based asymptomatic population.**

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Key words: Pulse wave velocity, Atherosclerosis, Carotid intima media thickness, Coronary artery calcium, Coronary artery stenosis

Introduction

Atherosclerosis has been associated with insidious vascular pathologies. After a latent period, atherosclerotic vessels can cause acute critical cerebrocardiac events, including stroke and acute myocardial infarction, as well as slightly stable medical conditions including dizziness and angina pectoris. Moreover, many clinical studies have demonstrated poor clinical outcomes in asymptomatic populations with subclinical atherosclerotic vascular changes[1, 2]. Therefore, early detection of atherosclerotic vascular changes before clinical manifestations is important to prevent future vascular events.

To examine atherosclerotic vascular change, many non-invasive imaging technologies have been introduced. Carotid ultrasound is used to examine atherosclerotic vascular changes of carotid arteries by measuring carotid intima media thickness (CIMT)

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and to detect carotid atherosclerotic plaques (CAP)[3, 4]. Coronary computed tomography (CT) is also used to examine coronary arteries by measuring coronary artery calcium (CAC) and coronary artery stenosis (CAS)[5-7]. Although these imaging modalities have the potential to accurately detect vascular atherosclerotic changes, discordance among CIMT, CAP, CAC, and CAS may cause some discrepancy in evaluating the overall atherosclerotic vascular burden. Moreover, high medical cost, use of a nephrotoxic contrast dye, and extensive radiation exposure limit their wide use in screening subclinical atherosclerotic vascular changes in the asymptomatic population[8].

Brachial-ankle pulse wave velocity (baPWV) is a non-invasive hemodynamic parameter that represents arterial stiffness[9, 10]. Arterial stiffness has been well-known to be associated with future cardiovascular events[11-13]. Previous studies have demonstrated that baPWV could be useful for screening subclinical atherosclerosis[14-16]. However, at present, little information is available on the relationship between these parameters and subclinical coronary and carotid atherosclerotic changes.

In this study, we investigated the differences among CIMT, CAP, CAC, and CAS and explored the potential role of baPWV to screen both carotid and coronary atherosclerotic changes in a community-based asymptomatic population.

Methods

Study Design

This study is a cross-sectional study derived from the community-based cohort study (Metabolic Syndrome Cohort in Korea, NCT02077530). In brief, between January 2014 and September 2014, 1500 metabolic syndrome subjects aged 31–64 years old and screened from a general population in 25 public healthcare centers were randomly recruited. Demographic data were obtained from the pre-screened participants, and subjects with a previous history of angina pectoris, myocardial infarction, stroke, or any revascularization were excluded from further examinations. In total, 1130 subjects took medical exams with self-questionnaire, blood tests, non-invasive hemodynamic measurement, and carotid ultrasonography on the first day of visit. Coronary CT was not performed in subjects with serum creatinine ≥ 1.5 mg/dL. Coronary CT was recommended to be performed within 4 weeks after the initial visit. After excluding subjects with missing data for any of those exams, 773 subjects were finally analyzed. The study was approved by the institutional review board of Korea University Anam Hospital (IRB NO. ED13087) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained.

baPWV and Augmentation Index

baPWV and ankle-brachial index (ABI) were measured using an oscillometric sphygmomanometer (VP-1000 plus; Omron Colin, Kyoto, Japan). Central systolic blood pressure (cSBP) and augmentation index (AIx) were measured using applanation tonometry (HEM9000A1; Omron Colin, Kyoto, Japan). The adjusted AIx value for a heart rate at 75 beats per min (AIx@75) was also reported. All measurements were performed by trained nurses in accordance with the manufacturer's recommendations.

Carotid Ultrasonography

Carotid artery imaging was obtained by experienced clinicians using a B-mod tomographic ultrasound system (VIVID Q, GE, USA) with a linear 6.0–13.0 MHz probe. Carotid intima media thickness (CIMT) was measured 1.0 cm distal to both common carotid artery bifurcations. The presence of carotid artery plaque was determined when the local CIMT was ≥ 1.5 mm or 50% of the surrounding area[17].

Coronary CT

For all subjects, cardiac CT examinations were performed using a second-generation dual-source CT scanner (Somatom Definition Flash; Siemens Healthcare, Forchheim, Germany) with a $2 \times 128 \times 0.6$ mm^3 section collimation and a 280 ms ration time. Initially, a CT scan was performed to evaluate coronary artery calcium score (CACS) with 120-kV tube voltage, 80-mAs effective tube current, and 3-mm section thickness. Thereafter, coronary CT angiography (CCTA) was performed with 100-kV tube voltage and 350-mAS effective tuber current. During CCTA, non-ionic contrast material (60–90 mL of iopamidol, 370 mg of iodine per milliliter, Iopamiro; Bracco Diagnostics, Milano, Italy) was intravenously injected at a rate of 5 mL/s, followed by 50 mL of saline solution. Radiation dose reduction strategies, including high-pitch mode, prospective electrocardiogram (ECG) triggered scan, and ECG-gated tube current modulation, were used whenever feasible. The total estimated radiation dose for cardiac CT examinations ranged from 3 to 15 mSv. Helical CT scan data were obtained with retrospective or prospective ECG gating. CT images were reconstructed immediately after completing the CT scan to identify motion-free coronary artery images. The CAC score, calculated according to modified Agatston units, was categorized as 0 (0 Agatston score), mildly increased (1–99), and moderately increased (≥ 100)[18, 19]. Coronary artery stenosis was

evaluated for the following four major coronary arteries: right coronary artery, left circumflex artery, left anterior descending artery, and left main artery. Coronary arteries with >50% diameter stenosis were considered significant CAS and counted[20].

Laboratory Tests

Venous blood samples were obtained after at least 8 h of fasting. Serum glucose level was measured using UV assay. Serum levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were measured using the homogeneous enzymatic colorimetric assay. High sensitive C-reactive protein (hsCRP), apolipoprotein A1, and apolipoprotein B were measured using the immunoturbidimetry assay. All laboratory measurements were performed by Green Cross Laboratories (Seoul, Korea).

Definitions

Based on the expert consensus and other previous reports, the composite coronary and carotid atherosclerosis was defined when coronary CT or carotid ultrasonographic findings met any one of the following four criteria: 1) CAS ≥ 50% diameter stenosis[21, 22], 2) CAC score ≥ 100[5, 23], 3) CIMT ≥ 0.9 mm[24], and 4) the presence of CAP[25].

Based on the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel Ⅲ (NCEP ATP Ⅲ)[26] and the Korean Society for the Study of Obesity definitions, metabolic syndrome was defined when any of the three factors met the following criteria: 1) waist circumference ≥ 90 cm for men and ≥ 80 cm for women, 2) triglycerides ≥ 150 mg/dL, 3) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, 4) blood pressure ≥ 130/85 mmHg, and 5) fasting glucose ≥ 100 mg/dL.

Statistical Analysis

Categorical variables were reported as count (percentage) and continuous variables as the mean ± standard deviation. Independence of categorical variables was analyzed by the chi-square test. Continuous variables were analyzed by the one-way ANOVA. The logistic regression model was used to identify risk predictors for each index and composite coronary and carotid atherosclerosis. The risk factors were tested with a multivariable logistic regression analysis by the backward selection method in male, female, and total population. The selection significance level was 0.1. The logistic regression results were expressed as the odds ratio with a 95% confidence interval and *p* value. Receiver operating characteristic (ROC) curves of baPWV were constructed for a diagnosis of each index and composite coronary and carotid atherosclerosis. An area under the curve (AUC) of 0.5 means a test of no diagnosis value. The optimal cut off point was calculated using youden index. All tests were two-tailed, and the *p* values <.05 were considered statistically significant. All statistical analyses were performed using SAS (v9.3, SAS institute Inc., USA).

Results

Baseline Clinical Characteristics

Demographic features are presented in **Table 1**. Study subjects were evenly divided into four groups according to baPWV. Subjects with higher baPWV were significantly older; predominantly male; and presented with a higher prevalence of hypertension, diabetes mellitus, and metabolic syndrome. Body mass index was lower in subjects with higher baPWV. Among the components of metabolic syndrome, blood pressure and serum glucose were associated with higher baPWV. Serum HDL cholesterol level was higher in subjects with higher baPWV. Serum hemoglobin and apolipoprotein A1 levels were also higher in subjects with higher baPWV. Other non-invasive hemodynamic parameters, including ABI, cSBP, Aix, and AIx@75, were also higher in subjects with higher baPWV.

Composite Coronary and Carotid Atherosclerosis

Coronary atherosclerosis was defined as a CAC score of ≥ 100 or a CAS of ≥ 50% of the stenosis diameter by coronary CT. Carotid atherosclerosis was defined as a CIMT of ≥ 0.9 mm or the presence of CAP in carotid ultrasonography. Although a CIMT of ≥ 0.9 mm was not significantly associated with higher baPWV, subjects with higher baPWV showed higher prevalence of a CAC score of ≥ 100 and a CAS of ≥ 50% of the stenosis diameter and CAP (**Table 2**). Therefore, subjects with a higher baPWV had a higher prevalence of composite coronary and carotid atherosclerosis determined by CAC score, CAS, CIMT, and CAP. Interestingly, only baPWV showed the significant relationship with the composite coronary and carotid atherosclerosis, and both AIx@75 and cSBP failed to show any statistical significance (**Fig. 1**). This suggested that baPWV could be a possible indicator for the composite coronary and carotid atherosclerosis and reflects their atherosclerotic burden.

Risk Predictors for Composite Coronary and Carotid Atherosclerosis

To investigate potential risk predictors for composite coronary and carotid atherosclerosis, univariate and multivariable logistic regression analyses were per-

Table 1. Baseline clinical characteristics

	Q1 (n = 194)	Q2 (n = 193)	Q3 (n = 193)	Q4 (n = 193)	p-value
Age (year)	51.40 ± 8.22	54.16 ± 6.83	55.27 ± 5.99	57.38 ± 5.58	< .001
Men	78 (40.21)	87 (45.08)	109 (56.48)	103 (53.37)	0.002
BMI	26.47 ± 3.01	25.60 ± 2.63	25.71 ± 2.96	25.08 ± 2.81	< .001
Current smoking	38 (19.59)	29 (15.1)	43 (22.28)	46 (23.96)	0.140
Hypertension	39 (20.1)	57 (29.53)	91 (47.15)	120 (62.18)	< .001
Diabetes	24 (12.37)	18 (9.33)	25 (12.95)	45 (23.32)	0.001
Dyslipidemia	70 (36.08)	73 (37.82)	68 (35.23)	72 (37.31)	0.944
Metabolic syndrome components					
Waist (cm)	88.31 ± 8.07	87.18 ± 7.59	87.88 ± 7.68	86.56 ± 7.63	0.124
Systolic BP (mmHg)	119.05 ± 11.89	123.83 ± 12.31	130.56 ± 13.52	137.70 ± 14.02	< .001
Diastolic BP (mmHg)	77.18 ± 8.68	80.18 ± 8.45	84.88 ± 9.10	87.46 ± 9.21	< .001
Triglyceride (mg/dL)	145.78 ± 93.90	161.18 ± 88.63	156.26 ± 98.69	158.16 ± 102.01	0.42
HDL-cholesterol (mg/dL)	50.12 ± 11.09	50.37 ± 13.06	51.87 ± 13.74	53.49 ± 12.70	0.034
Glucose (mg/dL)	96.91 ± 11.36	98.88 ± 11.84	100.78 ± 21.60	104.75 ± 22.76	< .001
Metabolic syndrome	59 (30.41)	79 (40.93)	73 (37.82)	87 (45.08)	0.009
Other laboratory findings					
Hemoglobin (g/dL)	14.01 ± 1.26	14.18 ± 1.35	14.45 ± 1.35	14.51 ± 1.24	< .001
Total cholesterol (mg/dL)	197.06 ± 32.06	202.05 ± 34.91	197.22 ± 35.07	204.88 ± 35.64	0.068
LDL-cholesterol (mg/dL)	130.25 ± 30.23	132.16 ± 34.07	127.18 ± 33.90	132.69 ± 33.80	0.350
hsCRP (mg/dL)	1.64 ± 3.51	1.73 ± 7.89	1.15 ± 1.46	1.47 ± 2.34	0.612
Apolipoprotein A1 (mg/dL)	138.92 ± 20.42	141.30 ± 23.99	143.39 ± 25.10	147.57 ± 24.53	0.003
Apolipoprotein B (mg/dL)	101.23 ± 21.61	104.11 ± 22.63	99.95 ± 24.68	104.41 ± 23.32	0.160
Non-invasive hemodynamic parameters					
baPWV (mean, cm/sec)	1150.24 ± 71.87	1296.77 ± 33.47	1420.53 ± 37.61	1681.73 ± 173.90	< .001
ABI (mean)	1.07 ± 0.09	1.08 ± 0.08	1.09 ± 0.09	1.11 ± 0.08	< .001
cSBP (mmHg)	122.05 ± 13.42	128.58 ± 13.54	135.16 ± 15.50	143.14 ± 16.38	< .001
AIx	74.61 ± 16.47	78.62 ± 15.16	78.23 ± 15.14	80.13 ± 13.63	0.003
AIx@75	74.75 ± 13.51	78.08 ± 12.47	78.31 ± 12.34	80.49 ± 10.71	< .001
Coronary artery calcium (CAC) and carotid intima medial thickness (CIMT)					
CAC score	9.68 ± 44.51	12.92 ± 46.58	15.59 ± 55.72	29.28 ± 110.92	0.033
CIMT (mean, mm)	0.62 ± 0.11	0.65 ± 0.13	0.65 ± 0.11	0.69 ± 0.11	< .001

Data are presented as the mean ± SD for continuous variables and the number (%) for categorical variables. BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index; cSBP, central systolic blood pressure; AIx, augmentation index; AIx@75, augmentation index at 75 beats/min.

Table 2. baPWV and other index atherosclerosis (CAC score, CAS, CIMT, CAP and their composite)

	Q1 (n = 194)	Q2 (n = 193)	Q3 (n = 193)	Q4 (n = 193)	p-value
CAC score ≥ 100	4 (2.06)	6 (3.11)	10 (5.18)	11 (5.7)	0.040
CAS ≥ 50%	24 (12.37)	31 (16.06)	37 (19.17)	38 (19.69)	0.037
CIMT ≥ 0.9 mm	3 (1.55)	9 (4.66)	5 (2.59)	9 (4.66)	0.209
Presence of CAP	14 (7.25)	13 (6.77)	21 (10.94)	32 (16.67)	0.001
Composite coronary and carotid atherosclerosis	41 (21.13)	48 (24.87)	61 (31.61)	68 (35.23)	0.001

Data are presented as the number (%). CAC, coronary artery calcium; CAS, coronary artery stenosis; CIMT, carotid intima media thickness; CAP, carotid artery plaque.

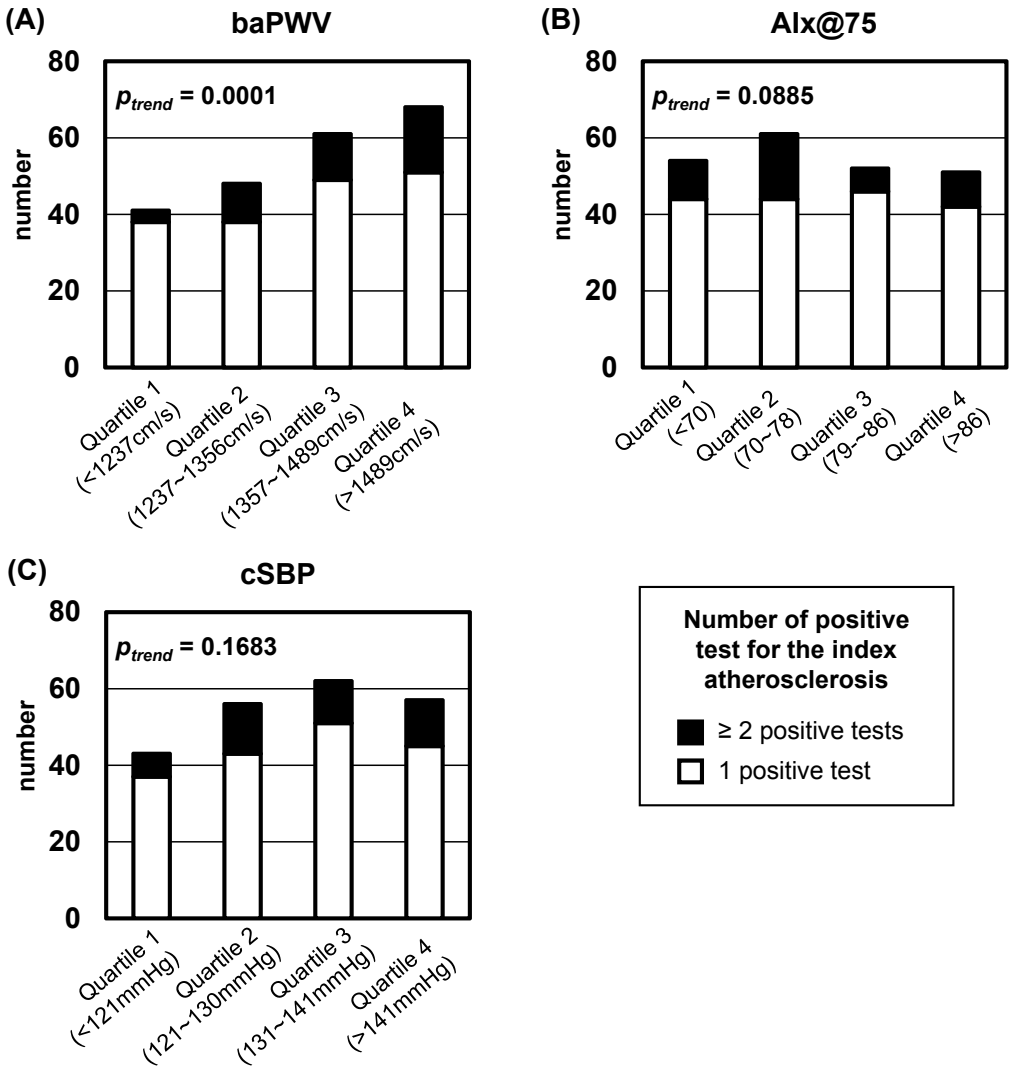


Fig. 1. baPWV, AIx@ and cSBPon the composite atherosclerotic burden

baPWV, brachial-ankle pulse wave velocity; AIx@75, augmentation index at 75 beats/min; cSBP, central systolic blood pressure.

formed (**Table 3**). In total population, univariate analyses suggested that age, male gender, current smoking habits, diabetes mellitus, systolic blood pressure, serum triglyceride, HDL cholesterol, glucose, and baPWV were the potential risk predictors for the composite coronary and carotid atherosclerosis. Multivariable analyses proposed age, male gender, diabetes mellitus, serum HDL cholesterol, and apolipoprotein A1 levels as significant independent risk predictors for the composite coronary and carotid atherosclerosis. In subgroup analyses, age, LDL cholesterol, and apolipoprotein-B in male and age, hypertension, diastolic blood pressure, and triglyceride in female were revealed as significant risk predictors. baPWV failed to be presented as a significant independent risk predictor for the composite coronary and carotid atherosclerosis in male, female, and total population. Interestingly, multivariable logistic regression analyses for each index atherosclerosis demonstrated baPWV as a significant independent risk factor for CAP in male and total population. AIx@75 showed a rather inverse relationship (OR, 0.6669) for CAP in male. Thus, although baPWV was not proposed as a statistically significant independent risk predictor for composite atherosclerosis, baPWV could be considered as the most significant indicator for atherosclerosis (CAP at least) among the non-invasive hemodynamic parameters (baPWV, AIx@75, and cSBP).

Table 3. Logistic regression analyses for the composite coronary and carotid atherosclerosis (total population)

Risk Factor	Total population											
	Composite endpoint				CAC score ≥ 100		CIMT ≥ 0.9mm		Presence of CAP		CAS ≥ 50%	
	Univariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.57 (1.31-1.89)	<.001	1.71 (1.41-2.07)	<.001	3.02 (1.72-5.31)	<.001	2.32 (1.28-4.19)	0.005	1.34 (1.00-1.79)	0.048	1.54 (1.23-1.93)	<.001
Male	2.22 (1.61-3.1)	<.001	2.25 (1.59-3.17)	<.001	3.68 (1.26-10.78)	0.018	2.70 (1.12-6.49)	0.026	2.98 (1.77-5.03)	<.001	2.41 (1.46-3.99)	0.001
BMI	0.95 (0.81-1.11)	0.495							0.74 (0.56-0.97)	0.029	1.54 (1.07-2.20)	0.020
Current smoking	1.46 (1.00-2.12)	0.050			2.77 (1.21-6.34)	0.016						
Hypertension	1.28 (0.93-1.76)	0.124										
Diabetes mellitus	1.81 (1.19-2.75)	0.005	1.56 (1.01-2.41)	0.047								
Dyslipidemia	1.23 (0.88-1.68)	0.233									1.50 (1.00-2.22)	0.048
Waist	1.10 (0.94-1.29)	0.244									0.63 (0.42-0.94)	0.024
Systolic BP	1.19 (1.02-1.39)	0.030										
Diastolic BP	1.17 (1.00-1.37)	0.053										
Triglyceride	1.19 (1.03-1.38)	0.021					0.20 (0.07-0.60)	0.004				
HDL-Cholesterol	0.8 (0.68-1.38)	0.011	0.61 (0.44-0.83)	0.002	1.37 (0.96-1.98)	0.086	0.11 (0.03-0.48)	0.003			0.53 (0.36-0.78)	0.001
Glucose	1.24 (0.06-1.44)	0.007										
LDL-cholesterol	0.93 (0.80-1.09)	0.377										
hsCRP	0.88 (0.67-1.16)	0.377										
Apolipoprotein A1	0.95 (0.81-1.12)	0.554	1.46 (1.08-1.97)	0.014			5.78 (1.85-18.07)	0.003			1.63 (1.15-2.32)	0.006
Apolipoprotein B	1.09 (0.93-1.28)	0.284			2.76 (1.09-7.00)	0.033	1.45 (0.95-2.21)	0.086				
baPWV	1.4 (1.20-1.63)	<.001							1.38 (1.10-1.74)	0.005		
cSBP	1.09 (0.93-1.27)	0.293										
AIx@75	0.90 (0.77-1.06)	0.202										

BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; baPWV, brachial-ankle pulse wave velocity; cSBP, central systolic blood pressure; AIx@75, augmentation index at 75 beats/min; OR, odd ratio; 95%CI, 95% confidence interval

Table 3. Logistic regression analyses for the composite coronary and carotid atherosclerosis (men)

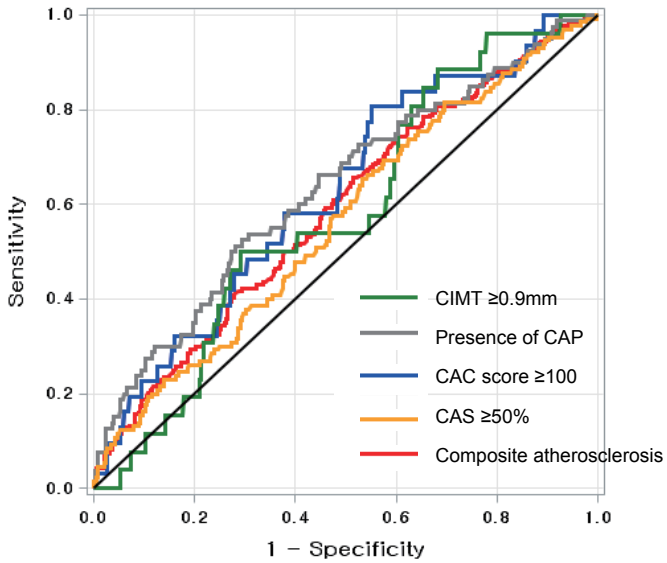
Risk Factor	Total population											
	Composite endpoint				CAC score ≥ 100		CIMT ≥ 0.9 mm		Presence of CAP		CAS ≥ 50%	
	Univariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.78 (1.39-2.28)	<.001	1.83 (1.42-2.37)	<.001	4.52 (2.11-9.57)	<.001	3.04 (1.39-6.68)	0.006	1.58 (1.05-2.38)	0.027	1.58 (1.17-2.14)	0.003
BMI	0.95 (0.77-1.18)	0.665									1.26 (0.96-1.64)	0.091
Current smoking	1.00 (0.65-1.53)	0.990			3.26 (1.37-7.75)	0.008						
Hypertension	1.35 (0.89-2.05)	0.164			2.59 (1.06-6.31)	0.036			3.27 (1.60-6.65)	0.001		
Diabetes mellitus	1.59 (0.93-2.72)	0.092										
Dyslipidemia	1.06 (0.68-1.65)	0.800					0.28 (0.07-1.14)	0.075				
Waist	0.91 (0.74-1.13)	0.406							0.70 (0.50-0.99)	0.042		
Systolic BP	1.00 (0.81-1.24)	0.969							0.65 (0.44-0.97)	0.033		
Diastolic BP	0.95 (0.77-1.17)	0.603					0.54 (0.31-0.94)	0.030				
Triglyceride	1.05 (0.85-1.29)	0.653										
HDL-Cholesterol	0.92 (0.74-1.14)	0.450										
Glucose	1.17 (0.95-1.45)	0.144										
LDL-cholesterol	0.89 (0.72-1.10)	0.299	0.52 (0.32-0.83)	0.007	0.41 (0.16-1.06)	0.065			0.49 (0.25-0.93)	0.030	0.55 (0.32-0.94)	0.030
hsCRP	0.83 (0.62-1.11)	0.209										
Apolipoprotein A1	1.05 (0.85-1.30)	0.635										
Apolipoprotein B	1.02 (0.83-1.26)	0.854	1.95 (1.21-3.13)	0.006	2.26 (0.87-5.87)	0.093	1.68 (0.95-2.96)	0.077	2.10 (1.09-4.04)	0.026	1.80 (1.05-3.08)	0.032
baPWV	1.33 (1.08-1.64)	0.008							1.59 (1.13-2.24)	0.008		
cSBP	1.01 (0.82-1.25)	0.911										
AIx@75	1.13 (0.91-1.40)	0.259							0.67 (0.47-0.95)	0.023		

BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; baPWV, brachial-ankle pulse wave velocity; cSBP, central systolic blood pressure; AIx@75, augmentation index at 75 beats/min; OR, odd ratio; 95%CI, 95% confidence interval

Table 3. Logistic regression analyses for the composite coronary and carotid atherosclerosis (women)

Risk Factor	Total population											
	Composite endpoint				CAC score ≥ 100		CIMT ≥ 0.9 mm		Presence of CAP		CAS ≥ 50%	
	Univariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.6 (1.19-2.16)	0.002	1.77 (1.29-2.44)	0.001			2.47 (0.86-7.10)	0.093	1.63 (0.93-2.87)	0.089	1.59 (1.11-2.27)	0.011
BMI	0.83 (0.64-1.07)	0.149							0.59 (0.36-0.97)	0.036		
Current smoking	0.42 (0.05-3.38)	0.417										
Hypertension	0.84 (0.49-1.44)	0.526	0.5 (0.27-0.93)	0.029					0.25 (0.08-0.80)	0.020		
Diabetes mellitus	1.85 (0.93-3.66)	0.078	2.06 (1.00-4.26)	0.051					2.65 (0.88-7.98)	0.083		
Dyslipidemia	1.62 (0.99-2.64)	0.056										
Waist	0.89 (0.69-1.14)	0.338	0.78 (0.59-1.02)	0.072							0.76 (0.55-1.05)	0.095
Systolic BP	1.31 (1.03-1.66)	0.027										
Diastolic BP	1.35 (1.05-1.72)	0.018	1.74 (1.30-2.33)	<.001			2.45 (1.17-5.12)	0.018	2.13 (1.33-3.42)	0.002	1.39 (1.02-1.89)	0.037
Triglyceride	1.2 (0.96-1.50)	0.105	1.32 (1.02-1.70)	0.035			0.06 (0.01-0.52)	0.011			1.54 (1.18-2.02)	0.002
HDL-Cholesterol	0.8 (0.62-1.04)	0.096			143.93 (6.53-3171.64)	0.002	0.02 (0.00-0.34)	0.007				
Glucose	1.17 (0.94-1.47)	0.161										
LDL-cholesterol	1.08 (0.84-1.38)	0.543			0.02 (0.00-0.96)	0.048						
hsCRP	0.97 (0.73-1.29)	0.818										
Apolipoprotein A1	0.88 (0.69-1.13)	0.330			0.009 (0.00-0.18)	0.002	17.18 (1.78-165.66)	0.014				
Apolipoprotein B	1.16 (0.91-1.48)	0.225			74.51 (1.88-2960.02)	0.022						
baPWV	1.38 (1.09-1.74)	0.007										
cSBP	1.25 (0.99-1.59)	0.063										
AIx@75	1.02 (0.80-1.30)	0.672			0.34 (0.11-1.01)	0.053					0.73 (0.53-1.00)	0.053

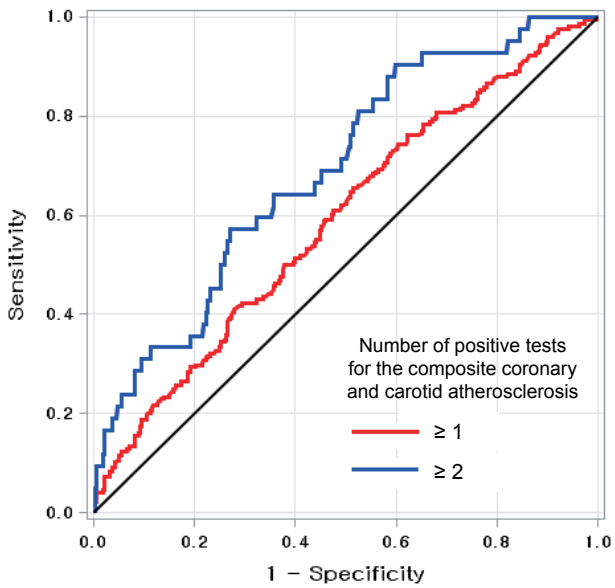
BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; baPWV, brachial-ankle pulse wave velocity; cSBP, central systolic blood pressure; AIx@75, augmentation index at 75 beats/min; OR, odd ratio; 95%CI, 95% confidence interval



	AUC (95% CI)
CIMT ≥ 0.9mm	0.582 (0.4828-0.6820)
Presence of CAP	0.634 (0.5672-0.7014)
CAC score ≥ 100	0.626 (0.5278-0.7241)
CAS ≥ 50%	0.565 (0.5114-0.6189)
the composite coronary and carotid atherosclerosis	0.589 (0.5447-0.6334)

AUC: area under the curve. 95% CI: 95% confidence interval.

Fig. 2. Comparison of baPWV receiver operating characteristic curves (ROCs) to detect CIMT ≥ 0.9 mm, presence of CAP, CAC score ≥ 100, CAS ≥ 50%, and their composite atherosclerosis



Number of positive tests for the composite coronary and carotid atherosclerosis		
≥ 1	AUC (95% CI)	0.589 (0.5447-0.6334)
	Cut-off value	1347.5
	Sensitivity	0.6101
	Specificity	0.5243
≥ 2	AUC (95% CI)	0.692 (0.6127-0.7709)
	Cut-off value	1413.5
	Sensitivity	0.6429
	Specificity	0.6432

AUC: area under the curve. 95% CI: 95% confidence interval.

Fig. 3. Comparison of baPWV ROCs depending on the number of positive tests for the composite coronary and carotid atherosclerosis

Diagnostic Potential of baPWV for the Composite Coronary and Carotid Atherosclerosis

We investigated the diagnostic potential of baPWV to detect subclinical coronary and carotid atherosclerosis (**Fig. 2** and **3**). For CIMT ≥ 0.9 mm, AUC for baPWV was 0.582 (95% CI, 0.4828–0.6820); for the presence of CAP, AUC was 0.634 (0.5672–0.7014); for CAC score ≥ 100, AUC was 0.626 (0.5278–0.7241); for CAS ≥ 50%, AUC was 0.565 (0.5114–0.6189); and for composite coronary and carotid atherosclerosis, AUC was 0.589 (0.5447–0.6334). For more than two positive tests for composite atherosclerosis, AUC was improved to 0.692 (0.6127–0.7709). A baPWV threshold >1413.5 cm/s had a sensitivity of 64.29% and a specificity of 64.32% for predicting more than two positive tests.

Discussion

The main findings of this study are as follows: (1) In total, 28.2% of asymptomatic subjects with previously screened metabolic syndrome met at least one of the composite coronary and carotid atherosclerosis criteria (CIMT ≥ 0.9 mm, CAC ≥ 100, or the presence of CAP or CAS). (2) Subjects with higher baPWV had a significantly higher prevalence of composite coronary and carotid atherosclerosis. (3) Multivariable logistic regression analyses failed to show baPWV as an independent risk predictor for the composite coronary and carotid atherosclerotic change. (4) However, baPWV had moderate diagnostic potential to detect more than two positive tests in composite coronary and carotid atherosclerosis.

The Prevalence of Subclinical Atherosclerosis

Early screening and treatment for high risk asymptomatic subjects has been an important challenge for preventing future cerebro-cardiovascular events. Although conventional risk factors (smoking, hypertension, diabetes, hypertension, and dyslipidemia) are important for the development of atherosclerosis, these risk factors have a limited ability to predict atherosclerotic burden in an asymptomatic population[27]. At least 10%–15% of subjects with overt coronary heart disease have no major risk factors[28]. Previous observational cohort studies for primary prevention showed varied prevalence (ranged from 40% to 90%) of subclinical atherosclerosis depending on the definition[29-31]. This study adopted more stringent definitions of subclinical atherosclerosis compared with previous studies, and the composite prevalence of both coronary and carotid atherosclerosis was 28.2%. In this study, the prevalence of subclinical atherosclerosis determined by CAS was significantly higher than that determined by CAC, CAP, or CIMT (**Supplemental Fig. 1**). Considering that the prevalence of significant CAS (stenosis diameter >50%) was reported to be 5%–15% in an asymptomatic population and the suggested optimal cut-off value of CAC score for the significant CAS was 7.7, our data were consistent with those of previous studies[32, 33].

Association between Carotid and Coronary Atherosclerosis

Current guidelines recommend tests for subclinical atherosclerosis (CAC score, CIMT, etc.) for subjects with intermediate or uncertain risk[34]. Although various subclinical atherosclerosis tests have large overlaps, some tests can have discrepant positive and negative results. Selecting an atherosclerosis test and clinical implementation of aggressive risk reduction intervention could be ambiguous. Moreover, although atherosclerosis is mainly a panvascular process, carotid and coronary atherosclerosis can be associated with distinct clinical events of coronary heart disease and stroke. Yan EY *et al*. reported that carotid atherosclerosis determined by vascular stiffness was associated with the development of ischemic stroke but not coronary artery disease[35]. In contrary, Polak JF *et al*. demonstrated that carotid atherosclerosis determined by CIMT was associated with future coronary artery disease[36]. Recently, Gepner AD *et al*. also showed that coronary heart disease was associated with both CAC and CAP, and stroke was associated with CAP but not CAC[37]. These findings suggest that each testing modality reflects a different atherosclerotic burden, and screening for both coronary and carotid atherosclerosis could be beneficial. In this study, the presence of CAP was significantly associated with a higher CAC score and CAS (**Supplemental Table 1**). Higher CIMT was also significantly associated with higher CAC score but not with CAS. It suggested the significant association between carotid and coronary atherosclerosis.

Role of baPWV to Evaluate the Composite Coronary and Carotid Atherosclerosis

The main hypothesis in this study was that baPWV could predict the overall atherosclerotic burden involving both the coronary and carotid arteries. Previously, baPWV has been reported to be associated with both coronary and carotid atherosclerosis. Chae MJ *et al*. showed that baPWV was associated with angiographically significant coronary artery disease[14]. Matsumoto M *et al*. also revealed that baPWV was associated with cerebrovascular lesions determined by magnetic resonance angiography[15]. This study revealed that subjects with higher baPWV had higher CAC score and CIMT and higher prevalence of CAP and CAS (**Tables 1** and **2**). The prevalence and extent of the composite coronary and carotid atherosclerosis was also higher in subjects with higher baPWV (**Fig. 1** and **Supplemental Fig. 1**). These data suggested that baPWV reflects both coronary and carotid atherosclerotic changes.

However, multivariable analysis failed to present baPWV as an independent risk predictor for the composite atherosclerotic change (**Table 3**). These results could be explained as that baPWV could reflect the overall atherosclerotic burden, which is driven by the conventional atherosclerosis risk factors, rather than independently affect the composite atherosclerotic change. Indeed, multivariable logistic regression analyses in this study suggested that age, blood pressure, and serum glucose level were significantly associated

with baPWV (data not shown). Previous studies also reported the significant relationship between baPWV and glycemic control, new-onset diabetes, and its vascular complications[38-41].

Finally, we explored the overall diagnostic potential of baPWV for composite coronary and carotid atherosclerosis (**Fig. 2** and **3**). Considering that various factors affect the development and progression of atherosclerosis, the ability of baPWV to detect and predict subclinical atherosclerosis may not be high. Previous studies also showed the limited diagnostic and prognostic potential of baPWV for cardiovascular diseases and clinical events[42, 43]. In this study, AUC for baPWV had limited value (0.589) to detect more than one positive test for composite coronary and carotid atherosclerosis determined by carotid ultrasonography (CIMT and CAP) and coronary CT angiography (CAC score and CAS). However, the predictive value improved to 0.692 to detect more than two positive tests. Thus, higher baPWV may have clinical implications for further evaluation of subclinical atherosclerosis. A recent study showed an additive role of baPWV for predicting future cardiovascular events when combined with other tests[44, 45].

Some limitations of this study should be considered. First, this study is a cross-sectional study. Although CAS, CAC score, CIMT, and CAP in this study have been known to be associated with future cerebrocardiovascular events, the direct causality between baPWV and future clinical coronary and carotid atherosclerotic events such as myocardial infarction and stroke cannot be determined. Previously, Lee HS *et al*. suggested baPWV as an significant predictor for future cardiovascular events[46]. Temporal relationship of baPWV and the development of those clinical events should be further investigated in future studies. Second, non-invasive hemodynamic parameters, including baPWV, AIx, and cSBP, were measured only once. Although the well-trained nurses measured those parameters with the strict protocol, it may act as a confounding factor in the results of the study. Third, the enrolled population in this study was recruited from subjects who had been taken care for metabolic syndrome in the public healthcare centers. Therefore, extrapolating the findings of this study to the populations such as those without metabolic syndrome or those with higher risk profiles (diabetes mellitus and chronic kidney disease) may be difficult, and further studies of various study populations are needed.

Conclusion

In a community-based population, baPWV was significantly higher in asymptomatic individuals with the composite coronary and carotid atherosclerotic changes, as determined by coronary CT and carotid ultrasonography. Without the independent relationship between baPWV and the composite atherosclerotic change, baPWV provided the modest diagnostic potential for the composite coronary and carotid atherosclerotic change.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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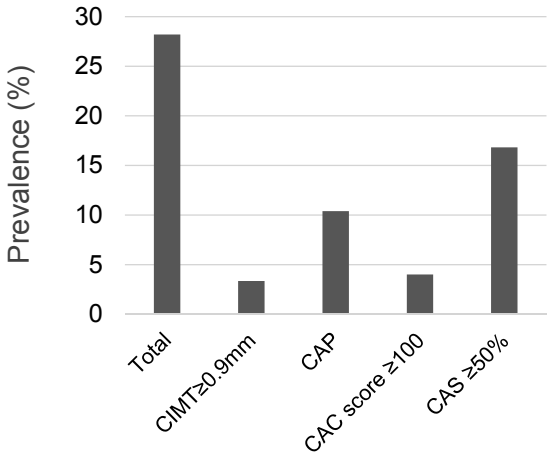

Supplemental Fig. 1. Prevalence of subclinical atherosclerosis

CAC, coronary artery calcium; CAS, coronary artery stenosis; CIMT, carotid intima media thickness; CAP, carotid artery plaque.

Supplemental Table 1. Correlation between coronary and carotid atherosclerosis

	CAC score			*p*-value
	0	1-99	≥ 100	
CIMT ≥ 0.9 mm	12 (2.07)	13 (8.02)	1 (3.23)	0.005
Presence of CAP	44 (7.61)	25 (15.53)	11 (36.67)	< .001
	CAS (%)			*p*-value
	< 30	30-50	≥ 50	
CIMT ≥ 0.9 mm	12 (2.45)	9 (5.84)	5 (3.85)	0.186
Presence of CAP	39 (8.04)	22 (14.29)	19 (14.62)	0.009

Data are presented as the number (%). CAC, coronary artery calcium; CAS, coronary artery stenosis; CIMT, carotid intima media thickness; CAP, carotid artery plaque.