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# Association of changes of pulse wave velocity and augmentation index after isometric handgrip exercise with coronary lesion extent and revascularization

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## Abstract

**Background:** Arterial stiffness is associated with myocardial ischemia and incident coronary artery disease (CAD), and indexes of arterial stiffness are usually increased in patients with CAD. However, these indexes are often increased in elderly without CAD. Arterial stiffness in patients with CAD may become more evident after isometric handgrip exercise which increases systolic pressure and ventricular afterload. We investigated the association of the change of stiffness indexes after isometric handgrip exercise with the lesion extent of CAD and the necessity for coronary revascularization.

**Methods:** Patients who were scheduled a routine coronary angiography via a femoral artery were enrolled. Arterial waveforms were traced at aortic root and external iliac artery using coronary catheters at baseline and 3 min after handgrip exercise. Augmentation index (AIx) was measured on the recorded aortic pressure waveform, and pulse wave velocity (PWV) was calculated using the ECG-gated time difference of the upstroke of arterial waveforms and distance between aortic root and external iliac artery.

**Results:** Total 37 patients were evaluated. Both PWV and AIx increased after handgrip exercise.  $\Delta$ PWV was significantly correlated with  $\Delta$ AIx ( $r = 0.344$ ,  $P = 0.037$ ). Patients were divided into higher and lower  $\Delta$ PWV or  $\Delta$ AIx groups based on the median values of 0.4 m/sec and 3.3%, respectively. Patients with higher PWV had more 2- or 3-vessel CAD (69% vs. 27%,  $P = 0.034$ ), and underwent percutaneous coronary intervention (PCI) more frequently (84% vs. 50%,  $P = 0.038$ ), but higher  $\Delta$ AIx was not associated with either the lesion extent or PCI. Area under curve (AUC) of  $\Delta$ PWV in association with PCI by C-statistics was 0.70 (95% confidence interval [CI] 0.51–0.88;  $P = 0.056$ ). In multiple logistic regression analysis,  $\Delta$ PWV was significantly associated with PCI (odds ratio 7.78; 95% CI 1.26–48.02;  $P = 0.027$ ).

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**Conclusions:** Higher  $\Delta$ PWV after isometric handgrip exercise was associated with the lesion extent of CAD and the necessity for coronary revascularization, but higher  $\Delta$ AIx was not.

**Keywords:** Arterial stiffness, Pulse wave velocity, Pulse wave analysis, Isometric exercise, Percutaneous coronary intervention

## Background

Normal or accelerated vascular aging and hypertension are two main factors determining arterial stiffness because they are basically related to the change of the arterial media [1]. However, diabetes, dyslipidemia, and smoking in addition to vascular aging and hypertension, all of which are shared common risk factors for coronary artery disease (CAD), may also change the mechanical properties of the arterial wall to make a stiff artery [2]. In a stiff arterial system, the velocities of the incident flow and the backward reflection flow are rapid enough for the early return of reflected waves during arterial systole rather than diastole, and the incident and reflected pressure waves are summed to increase aortic or central systolic pressure, but decrease central diastolic pressure, resulting in widened central pulse pressure [3]. Augmented central systolic pressure increases ventricular afterload and myocardial oxygen demand, and lowered diastolic pressure decreases coronary blood perfusion: the net results are myocardial ischemia and ventricular dysfunction [3–6]. For this reason, a stiff arterial system is associated with incident CAD, heart failure or stroke [7–9], and indexes of stiffness are related to the presence and severity of CAD [5]. Therefore, a stiff large artery is another feature of patients with CAD.

One of the popular methods evaluating arterial stiffness is measuring pulse wave velocity (PWV), a speed of an arterial pulsation through the arterial tree, usually between carotid and femoral arteries [6]. A number of studies reported that PWV was increased in patients with CAD, and correlated with the severity of coronary atherosclerosis [5, 10–14]. Increased aortic PWV (> 10 m/sec) is considered as a marker for detecting hypertension-mediated organ damage in guidelines for the management of arterial hypertension [15, 16]. Another method for measuring the arterial stiffness is central pulse wave analysis. Augmentation by the summation of incident and reflected waves in the aortic pressure waveform is expressed as augmentation pressure (AP) or augmentation index (AIx). AIx is a percentage of AP on aortic pulse pressure [3, 6]. The earlier studies showed that AIx was increased in patients with CAD and was associated with the severity of CAD, especially in younger patients (< 60 years of age) [10, 17, 18]. We already reported that AIx was negatively correlated with minimal luminal area of coronary atherosclerosis

measured by intravascular ultrasound, and was associated with coronary revascularization [19]. However, other studies showed no association of AIx with CAD, especially in elderly patients [8, 12, 20].

Increased PWV or AIx in patients with CAD may become more evident with a maneuver that influences the velocities of incident and reflected pressure waves. Isometric handgrip exercise, which increases systolic blood pressure (BP) and ventricular afterload [21–23], is a suitable and easily applicable tool for this purpose. The changes of PWV and AIx after isometric handgrip exercise may unmask the lesion extent and the necessity for coronary revascularization in elderly patients with CAD. In this study, the association of the change of PWV or AIx after isometric handgrip exercise with the lesion extent of CAD and the necessity for coronary revascularization was investigated.

## Methods

### Study patients

Patients who were scheduled a routine coronary angiography (CAG) via a femoral artery for the evaluation of the coronary atherosclerosis, and agreed to participate in the study were enrolled. Patients with acute coronary syndrome, or valvular heart disease were excluded. CAD was defined as  $\geq 70\%$  stenosis of the luminal diameter by the visual estimation of the operator in at least one major epicardial coronary artery or a past medical history of coronary revascularization. The extent of coronary atherosclerosis was classified as 1-, 2- or 3-vessel disease by the number of the major epicardial coronary arteries with a significant stenosis. Patients with a significant stenosis in the left main coronary artery were counted as having 2-vessel disease.

The study protocol was approved by the institutional review board of Jeju National University Hospital. Written informed consents were obtained from participating patients or legal representative.

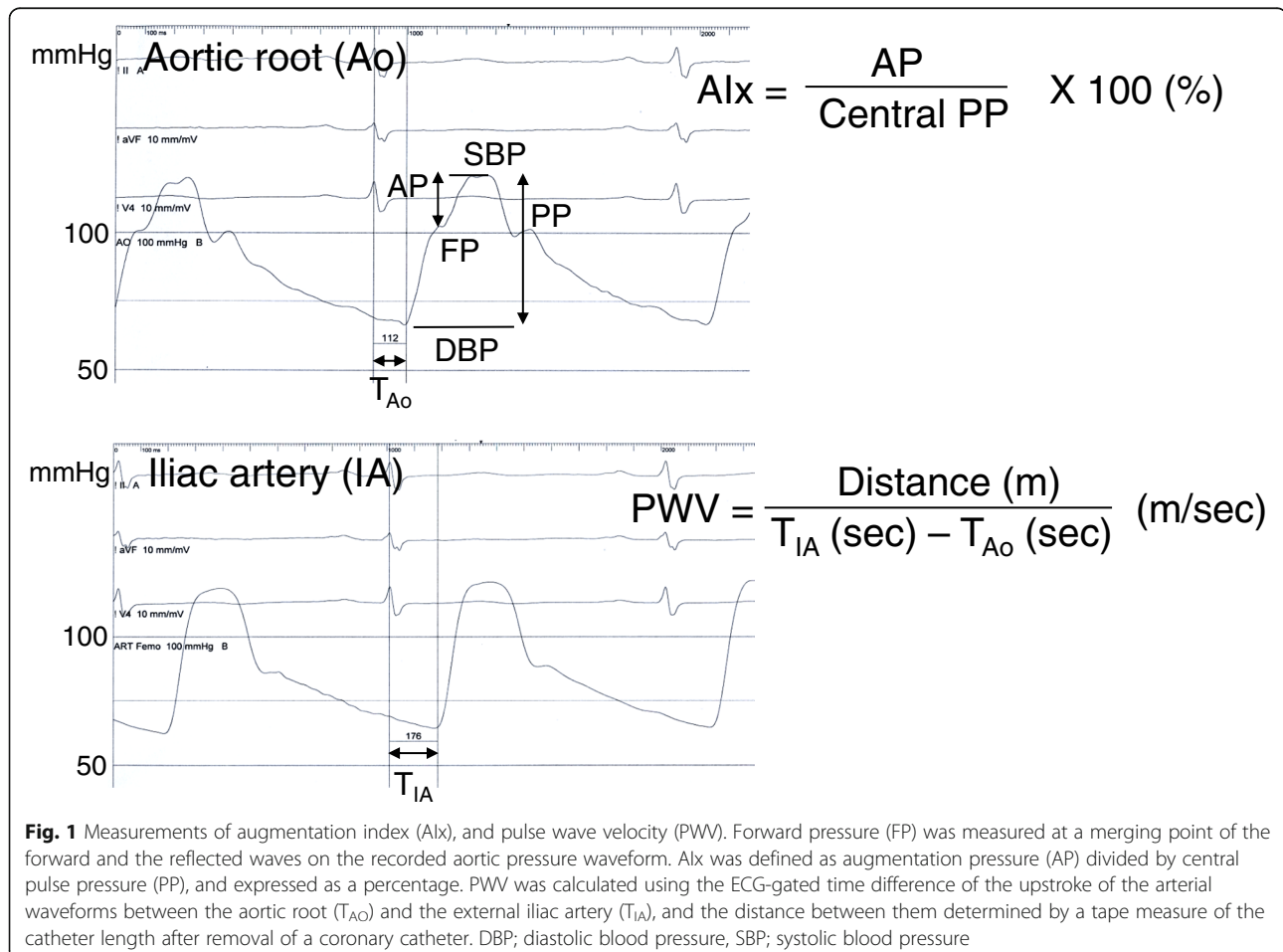
### Study protocol

The maximal voluntary forearm contraction power was measured with a JAMAR dynamometer (Sammons Preston Rolyan, Nottinghamshire, UK), and a submaximal target at 30 ~ 40% of maximal handgrip power was used for 3-min isometric handgrip exercise.

After routine CAG, arterial pressure waveforms were traced using a right coronary catheter and a fluid-filled pressure transducer system. Central arterial waveforms were recorded at the aortic root and traced before and at 1, 2 and 3 min after handgrip exercise. Forward pressure was measured at a merging point of the forward and the reflected waves on the recorded aortic pressure waveform. Augmentation pressure was defined as maximal central systolic pressure minus forward pressure. AIx was defined as augmentation pressure divided by central pulse pressure and expressed as a percentage (Fig. 1). Peripheral arterial waveforms were recorded at the external iliac artery before and after 3-min handgrip exercise. The ECG-gated time difference ( $\Delta$ Time) of the upstroke of the central and peripheral arterial waveforms was measured. The distance (D) between the aortic root and the external iliac artery was determined by a tape measure of the catheter length from the tip to the entry point at an arterial sheath minus the length of an arterial sheath (12 cm). PWV was defined as D divided by  $\Delta$ Time (Fig. 1) [24].

### Statistics

Data were expressed as mean  $\pm$  standard deviation for continuous variables, and as number (percentage) for categorical variables. Changes of hemodynamic parameters after handgrip exercise were analyzed using paired t-test, or where appropriate, Wilcoxon signed rank test. The association between changes of PWV ( $\Delta$ PWV) and AIx ( $\Delta$ AIx) after handgrip exercise was evaluated using correlation analysis. Patients were divided into higher and lower  $\Delta$ PWV or  $\Delta$ AIx groups based on the each median value. Data between groups were compared using unpaired t-test for continuous variables, and chi-square test for categorical variables. The association between higher  $\Delta$ PWV or  $\Delta$ AIx and coronary revascularization was evaluated using C-statistics and multiple logistic regression analysis after adjusting for age, gender, height, body mass index (BMI), hypertension, diabetes mellitus (DM) and chronic kidney disease (CKD). CKD was defined as estimated glomerular filtration rate  $< 60$  mL/min/1.73m<sup>2</sup> by Modification of Diet in Renal Disease equation.



**Table 1** Changes of hemodynamic parameters after isometric handgrip exercise ( $N = 37$ )

	Baseline	1 min	2 min	3 min
Heart rate (/min)	64.2 ± 9.2	67.5 ± 10.1*	68.9 ± 10.2*†	70.6 ± 12.9*†
Central systolic BP (mmHg)	118.4 ± 20.6	135.1 ± 21.4*	138.9 ± 22.5*†	140.4 ± 22.9*†
Central diastolic BP (mmHg)	63.4 ± 10.3	71.0 ± 10.6*	72.1 ± 11.3*†	72.7 ± 11.2*†
Central PP (mmHg)	55.0 ± 17.6	64.2 ± 18.2*	66.8 ± 19.2*†	67.7 ± 18.7*†
Forward pressure (mmHg)	108.7 ± 19.4	121.4 ± 20.7*	124.7 ± 21.8*†	126.2 ± 22.6*†
Augmentation pressure (mmHg)	9.7 ± 6.6	13.7 ± 8.3*	14.2 ± 8.5*	14.2 ± 8.7*
Augmentation index (%)	17.4 ± 10.5	21.2 ± 11.5*	21.5 ± 11.5*	21.4 ± 11.7*
Peripheral systolic BP (mmHg)	125.0 ± 20.4			140.7 ± 25.0*
Peripheral diastolic BP (mmHg)	62.2 ± 10.1			65.1 ± 10.3*
Peripheral PP (mmHg)	62.8 ± 18.4			75.7 ± 21.4*
Pulse wave velocity (m/sec)	9.99 ± 1.84			10.81 ± 2.33*

Values are mean ± standard deviation

\* $p < 0.05$  vs. baseline, † $p < 0.05$  vs. 1 min

BP Blood pressure, PP Pulse pressure

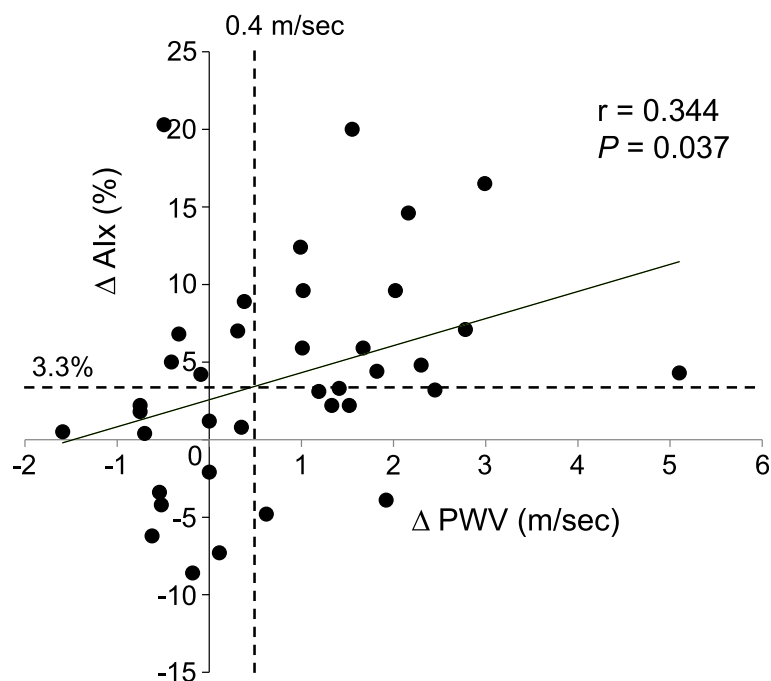
All statistical analyses were performed with the statistical package SPSS version 23 (IBM Co, Armonk, NY, US). Clinical significance was defined as  $P < 0.05$ .

## Results

Total 42 patients were enrolled. After excluding 4 patients without a definite inflection point of augmentation pressure on the central arterial waveform and 1 patient without a peripheral arterial waveform, final 37 patients were evaluated. The mean age of study patients was  $63.3 \pm 9.4$  years (range 41–82 years), 24 patients (65%)

were older than 60 years, 26 patients (70%) had hypertension, and 27 patients (73%) had CAD. Percutaneous coronary intervention (PCI) was conducted in 25 patients (68%): 1 year ago in 20 patients and on the day of the study in 5 patients. One patient underwent both PCI and coronary artery bypass graft.

Heart rate, central systolic and diastolic BP, central pulse pressure, forward pressure, augmentation pressure, and Alx increased progressively from 1 min after handgrip exercise, and reached the maximal level at 2 min. Peripheral systolic BP, diastolic BP, pulse pressure and



**Fig. 2** Correlation between changes of pulse wave velocity ( $\Delta$ PWV) and augmentation index ( $\Delta$ Alx) after isometric handgrip exercise. The median values of  $\Delta$ PWV and  $\Delta$ Alx were 0.4 m/sec and 3.3%, respectively

PWV also increased after 3-min handgrip exercise (Table 1).  $\Delta$ PWV was significantly correlated with  $\Delta$ AIx ( $r = 0.344$ ,  $P = 0.037$ ) (Fig. 2). The median values of  $\Delta$ PWV and  $\Delta$ AIx were 0.4 m/sec and 3.3%, respectively.

Patients were divided into higher and lower  $\Delta$ PWV ( $\geq 0.4$  vs.  $< 0.4$  m/sec) groups. Age, gender, BMI, smoker, co-morbid condition such as hypertension, DM, CKD or prior myocardial infarction, and medications were not significantly different between higher and lower  $\Delta$ PWV groups except hyperlipidemia. Patients with higher PWV had more 2- or 3-vessel CAD (69% vs. 27%,  $P = 0.034$ ). PCI was more frequently performed in patients with higher PWV (84% vs. 50%,  $P = 0.038$ ) (Table 2). Baseline hemodynamic parameters including PWV and AIx were not significantly different between two groups. After 3-min handgrip exercise, PWV,  $\Delta$ central systolic BP,  $\Delta$ AIx, and  $\Delta$ peripheral systolic BP were greater in patients with higher  $\Delta$ PWV (Table 3).

Patients were also divided into higher and lower  $\Delta$ AIx ( $\geq 3.3$  vs.  $< 3.3\%$ ) groups. Age, BMI, smoker, co-morbid condition such as hypertension, DM, hyperlipidemia,

CKD, prior myocardial infarction, or CAD, and medications except gender were not significantly different between higher and low  $\Delta$ AIx groups (Table 4). Patients with 2- or 3-vessel CAD were not significantly different (60% vs. 42%,  $P = 0.313$ ), and PCI was similarly performed in both groups (68% vs. 67%,  $P = 1.000$ ). Baseline central systolic BP and pulse pressure, augmentation pressure, AIx, peripheral systolic BP, and PWV were lower in higher  $\Delta$ AIx group. However, after 3-min handgrip exercise, these hemodynamic parameters became not significantly different between both groups (Table 5).

C-statistics showed the area under curve (AUC) of  $\Delta$ PWV in association with PCI was 0.70 (95% confidence interval [CI] 0.51–0.88;  $P = 0.056$ ). In contrast, it was 0.54 (95% CI 0.34–0.75;  $P = 0.685$ ) in case of  $\Delta$ AIx (Fig. 3). In multiple logistic regression analysis after adjustment,  $\Delta$ PWV was significantly associated with PCI (odds ratio [OR] 7.78; 95% CI 1.26–48.02;  $P = 0.027$ ), but  $\Delta$ AIx was not (OR 2.81; 95% CI 0.37–21.30;  $P = 0.318$ ).

**Table 2** Comparison of baseline characteristics according to the changes of pulse wave velocity after isometric handgrip exercise

	All patients (N = 37)	$\Delta$ PWV $\geq 0.4$ m/sec (N = 19)	$\Delta$ PWV $< 0.4$ m/sec (N = 18)	P value
Age (years)	63.3 $\pm$ 9.4	63.7 $\pm$ 8.4	62.9 $\pm$ 10.5	0.800
Male	23 (62)	14 (74)	9 (50)	0.184
Height (cm)	160.8 $\pm$ 8.9	162.0 $\pm$ 8.3	160.0 $\pm$ 9.6	0.422
Weight (kg)	65.7 $\pm$ 12.4	66.5 $\pm$ 12.1	64.9 $\pm$ 13.0	0.703
Body mass index (kg/m <sup>2</sup> )	25.27 $\pm$ 3.30	25.2 $\pm$ 3.0	25.3 $\pm$ 3.7	0.902
Smoker	9 (24)	5 (26)	4 (22)	0.459
Hypertension	26 (70)	14 (74)	12 (67)	0.728
Diabetes mellitus	8 (22)	5 (26)	3 (17)	0.693
Hyperlipidemia	33 (89)	19 (100)	14 (78)	0.046
Chronic kidney disease	19 (51)	9 (47)	10 (56)	0.746
Prior myocardial infarction	11 (30)	7 (37)	4 (22)	0.476
Coronary artery disease	27 (73)	16 (84)	11 (61)	0.151
CAG findings				0.051
1 vessel disease	13 (48)	5 (31)	8 (73)	0.034*
2 vessel disease	9 (33)	6 (38)	3 (27)	
3 vessel disease	5 (19)	5 (31)	0 (0)	
PCI	25 (68)	16 (84)	9 (50)	0.038
Medications				
Calcium channel blockers	16 (43)	10 (53)	6 (33)	0.325
RAS inhibitors	18 (49)	9 (47)	9 (50)	1.000
Beta-blockers	22 (60)	12 (63)	10 (56)	0.743
Nitrate	8 (22)	4 (21)	4 (22)	1.000
Statins	31 (84)	18 (95)	13 (72)	0.090

Values are mean  $\pm$  standard deviation or number (%)

\*1 vessel vs. 2- or 3-vessel disease

CAG Coronary angiography, PCI Percutaneous coronary intervention, PWV Pulse wave velocity, RAS Renin-angiotensin system

**Table 3** Comparison of hemodynamic parameters according to the changes of pulse wave velocity after isometric handgrip exercise

	$\Delta$ PWV $\geq 0.4$ m/sec (N = 19)	$\Delta$ PWV < 0.4 m/sec (N = 18)	P value
Isometric handgrip exercise			
Handgrip power, maximal (kg)	36.2 $\pm$ 13.2	31.0 $\pm$ 11.1	0.207
Handgrip power at exercise (kg)	13.3 $\pm$ 2.3	11.9 $\pm$ 3.3	0.134
Handgrip power %	38.9 $\pm$ 6.6	39.6 $\pm$ 5.8	0.736
Hemodynamic parameters, baseline			
Heart rate (/min)	62.5 $\pm$ 9.0	66.1 $\pm$ 9.3	0.240
Central systolic BP (mmHg)	114.3 $\pm$ 18.3	122.7 $\pm$ 22.4	0.216
Central diastolic BP (mmHg)	60.6 $\pm$ 7.1	66.4 $\pm$ 12.2	0.082
Central pulse pressure (mmHg)	53.7 $\pm$ 15.6	56.3 $\pm$ 19.8	0.660
Forward pressure (mmHg)	104.6 $\pm$ 17.3	113.1 $\pm$ 21.1	0.186
Augmentation pressure (mmHg)	9.7 $\pm$ 7.3	9.6 $\pm$ 5.9	0.974
Augmentation index (%)	17.9 $\pm$ 11.9	16.8 $\pm$ 9.2	0.742
Peripheral systolic BP (mmHg)	122.3 $\pm$ 19.4	127.8 $\pm$ 21.5	0.414
Peripheral diastolic BP (mmHg)	60.3 $\pm$ 7.7	64.2 $\pm$ 12.0	0.244
Peripheral pulse pressure (mmHg)	62.0 $\pm$ 17.3	63.6 $\pm$ 19.9	0.787
PWV (m/sec)	10.15 $\pm$ 2.07	9.83 $\pm$ 1.61	0.610
Exercise 3 min			
Heart rate (/min)	68.7 $\pm$ 13.9	72.7 $\pm$ 11.9	0.355
Central systolic BP (mmHg)	140.7 $\pm$ 20.9	140.1 $\pm$ 25.4	0.935
Central diastolic BP (mmHg)	70.7 $\pm$ 7.1	74.7 $\pm$ 14.2	0.289
Central pulse pressure (mmHg)	70.0 $\pm$ 18.0	65.3 $\pm$ 19.5	0.455
Forward pressure (mmHg)	124.1 $\pm$ 20.2	128.4 $\pm$ 25.3	0.567
Augmentation pressure (mmHg)	16.6 $\pm$ 9.3	11.7 $\pm$ 7.3	0.081
Augmentation index (%)	24.3 $\pm$ 12.4	18.3 $\pm$ 10.3	0.121
Peripheral systolic BP (mmHg)	144.3 $\pm$ 23.6	136.9 $\pm$ 26.5	0.377
Peripheral diastolic BP (mmHg)	65.7 $\pm$ 7.7	64.4 $\pm$ 12.7	0.708
Peripheral pulse pressure (mmHg)	78.6 $\pm$ 21.3	72.6 $\pm$ 21.6	0.395
PWV (m/sec)	12.03 $\pm$ 2.37	9.51 $\pm$ 1.44	< 0.001
$\Delta$ Central systolic BP (mmHg)	26.4 $\pm$ 10.3	17.3 $\pm$ 15.6	0.043
$\Delta$ Forward pressure (mmHg)	19.5 $\pm$ 7.5	15.3 $\pm$ 13.4	0.245
$\Delta$ Augmentation index (%)	6.3 $\pm$ 6.3	1.5 $\pm$ 6.8	0.033
$\Delta$ Peripheral systolic BP (mmHg)	22.1 $\pm$ 11.8	9.1 $\pm$ 8.7	0.001
$\Delta$ PWV (m/sec)	1.89 $\pm$ 1.00	-0.32 $\pm$ 0.49	< 0.001

Values are mean  $\pm$  standard deviation

BP Blood pressure, PWV Pulse wave velocity

## Discussion

The main result of this study is that, although a significant correlation was observed between  $\Delta$ PWV and  $\Delta$ AIx after isometric handgrip exercise, only higher  $\Delta$ PWV was associated with the lesion extent of CAD and the necessity for coronary revascularization.

Atherosclerosis is a generalized process of the arterial system including not only coronary arteries but also larger arteries. The atherosclerotic change of the aorta

makes the arterial system stiffer, and the stiff aorta is associated with myocardial ischemia and incident CAD [7–9]. Therefore, indexes of arterial stiffness are usually increased in patients with CAD. However, these indexes are often increased in elderly without CAD because systolic BP increases with aging, there is a close association between systolic BP and PWV, and both vascular aging and hypertension are the powerful factors determining arterial stiffness [1]. As a result, the difference of indexes



**Table 4** Comparison of baseline characteristics according to the changes of augmentation index after isometric handgrip exercise

	All patients (N = 37)	$\Delta\text{AIx} \geq 3.3\%$ (N = 19)	$\Delta\text{AIx} < 3.3\%$ (N = 18)	P value
Age (years)	63.3 ± 9.4	61.7 ± 10.4	65.0 ± 8.1	0.288
Male	23 (62)	15 (79)	8 (44)	0.045
Height (cm)	160.8 ± 8.9	162.6 ± 8.4	158.9 ± 9.3	0.213
Weight (kg)	65.7 ± 12.4	69.2 ± 13.1	62.1 ± 10.8	0.081
Body mass index (kg/m <sup>2</sup> )	25.27 ± 3.30	25.98 ± 3.17	24.51 ± 3.36	0.180
Smoker	9 (24)	5 (26)	4 (22)	0.124
Hypertension	26 (70)	13 (68)	13 (72)	1.000
Diabetes mellitus	8 (22)	3 (16)	5 (28)	0.447
Hyperlipidemia	33 (89)	18 (95)	15 (83)	0.340
Chronic kidney disease	19 (51)	8 (42)	11 (61)	0.330
Prior myocardial infarction	11 (30)	5 (26)	6 (33)	0.728
Coronary artery disease	27 (73)	15 (79)	12 (67)	0.476
CAG findings				0.620
1 vessel disease	13 (48)	6 (40)	7 (58)	0.313*
2 vessel disease	9 (33)	6 (40)	3 (25)	
3 vessel disease	5 (19)	3 (20)	2 (17)	
PCI	25 (68)	13 (68)	12 (67)	1.000
Medications				
Calcium channel blockers	16 (43)	10 (53)	6 (33)	0.325
RAS inhibitors	18 (49)	9 (47)	9 (50)	1.000
Beta-blockers	22 (60)	13 (68)	9 (50)	0.325
Nitrate	8 (22)	4 (21)	4 (22)	1.000
Statins	31 (84)	18 (95)	13 (72)	0.090

Values are mean ± standard deviation or number (%)

\*1 vessel vs. 2- or 3-vessel disease

AIx Augmentation index, CAG Coronary angiography, PCI Percutaneous coronary intervention, RAS Renin-angiotensin system

of arterial stiffness between patients with and without CAD may be not evident in elderly. The previous meta-analysis showed that aortic PWV was a predictor of future cardiovascular events such as CAD or stroke even in elderly, but its relation to cardiovascular events was weaker in older than younger patients, and the hazard ratio was decreased with age (1.89, 1.77, 1.36, and 1.23 for age ≤ 50, 51–60, 61–70, and > 70 years, respectively) [9]. The usefulness of AIx as a marker for CAD in older patients is even more unclear. Because AIx strongly correlates with age and it is also influenced by heart rate, body length or the pattern of ventricular ejection [3], AIx may not be an accurate index for arterial stiffness. The comparison of aortic PWV with AIx as a surrogate for the extent and severity of CAD was possible in one study that measured both indexes in the same patients at the time of coronary angiography. It showed the significant association of the extent and severity of CAD with PWV, but not with AIx [12].

Isometric handgrip exercise is a non-invasive and easily applicable maneuver to increase heart rate, BP and

left ventricular afterload [21–23]. In this study, central systolic BP, forward and augmentation pressures, AIx, peripheral BP and PWV were increased after handgrip exercise. Although  $\Delta\text{PWV}$  and  $\Delta\text{AIx}$  correlated each other, the pattern of  $\Delta\text{PWV}$  and  $\Delta\text{AIx}$  after handgrip exercise was different. Baseline PWV was not different between higher and lower  $\Delta\text{PWV}$  groups, but after 3-min handgrip exercise,  $\Delta$ central systolic BP,  $\Delta$ peripheral systolic BP and PWV were greater in higher  $\Delta\text{PWV}$  group. However, baseline AIx was smaller in higher  $\Delta\text{AIx}$  group, and AIx after 3-min handgrip exercise became similar between higher and lower  $\Delta\text{AIx}$  groups because of more increase of augmentation pressure in lower  $\Delta\text{AIx}$  group. All of these findings suggest that  $\Delta\text{AIx}$  may be larger in patients with lower baseline AIx regardless of arterial stiffness and reach plateau after handgrip exercise. Therefore,  $\Delta\text{AIx}$  after handgrip exercise may not be as a good index for arterial stiffness as  $\Delta\text{PWV}$ .

The mean age of patients of this study was 63.3 years, 65% were > 60 years and 70% of them had hypertension. These findings may be usually seen in patients with

**Table 5** Comparison of hemodynamic parameters according to the changes of augmentation index after isometric handgrip exercise

	$\Delta AIX \geq 3.3\%$ (N = 19)	$\Delta AIX < 3.3\%$ (N = 18)	P value
Isometric handgrip exercise			
Handgrip power, maximal (kg)	37.0 ± 14.4	30.1 ± 8.7	0.089
Handgrip power at exercise (kg)	13.5 ± 2.8	11.7 ± 2.7	0.060
Handgrip power %	38.7 ± 6.7	39.8 ± 5.6	0.566
Hemodynamic parameters, baseline			
Heart rate (/min)	65.7 ± 9.9	62.7 ± 8.4	0.334
Central systolic BP (mmHg)	109.9 ± 16.2	127.3 ± 21.3	0.008
Central diastolic BP (mmHg)	62.0 ± 8.4	65.0 ± 12.0	0.373
Central pulse pressure (mmHg)	48.0 ± 14.7	62.3 ± 17.7	0.011
Forward pressure (mmHg)	103.7 ± 15.8	114.1 ± 21.9	0.105
Augmentation pressure (mmHg)	6.2 ± 4.9	13.3 ± 6.2	< 0.001
Augmentation index (%)	13.3 ± 9.6	21.7 ± 10.0	0.013
Peripheral systolic BP (mmHg)	118.5 ± 19.3	131.8 ± 19.8	0.045
Peripheral diastolic BP (mmHg)	61.3 ± 8.3	63.2 ± 11.9	0.562
Peripheral pulse pressure (mmHg)	57.2 ± 17.8	68.6 ± 17.6	0.058
Pulse wave velocity (m/sec)	9.30 ± 1.72	10.72 ± 1.72	0.017
Exercise 3 min			
Heart rate (/min)	70.5 ± 13.4	70.8 ± 12.9	0.948
Central systolic BP (mmHg)	135.0 ± 19.7	146.1 ± 25.1	0.140
Central diastolic BP (mmHg)	71.5 ± 7.2	73.9 ± 14.4	0.527
Central pulse pressure (mmHg)	63.5 ± 18.7	72.2 ± 18.0	0.157
Forward pressure (mmHg)	120.9 ± 17.0	131.7 ± 26.7	0.154
Augmentation pressure (mmHg)	14.1 ± 9.1	14.4 ± 8.5	0.908
Augmentation index (%)	22.2 ± 11.6	20.4 ± 12.0	0.648
Peripheral systolic BP (mmHg)	136.2 ± 22.6	145.6 ± 27.1	0.259
Peripheral diastolic BP (mmHg)	64.5 ± 7.6	65.6 ± 12.8	0.754
Peripheral pulse pressure (mmHg)	71.6 ± 21.1	79.9 ± 21.4	0.242
Pulse wave velocity (m/sec)	10.68 ± 2.59	10.94 ± 2.10	0.747
$\Delta$ Central systolic BP (mmHg)	25.1 ± 11.7	18.8 ± 15.3	0.169
$\Delta$ Forward pressure (mmHg)	17.2 ± 7.8	17.7 ± 13.6	0.900
$\Delta$ Augmentation index (%)	9.0 ± 5.3	-1.3 ± 3.8	< 0.001
$\Delta$ Peripheral systolic BP (mmHg)	17.7 ± 11.2	13.7 ± 13.1	0.330
$\Delta$ Pulse wave velocity (m/sec)	1.38 ± 1.39	0.21 ± 1.08	0.008

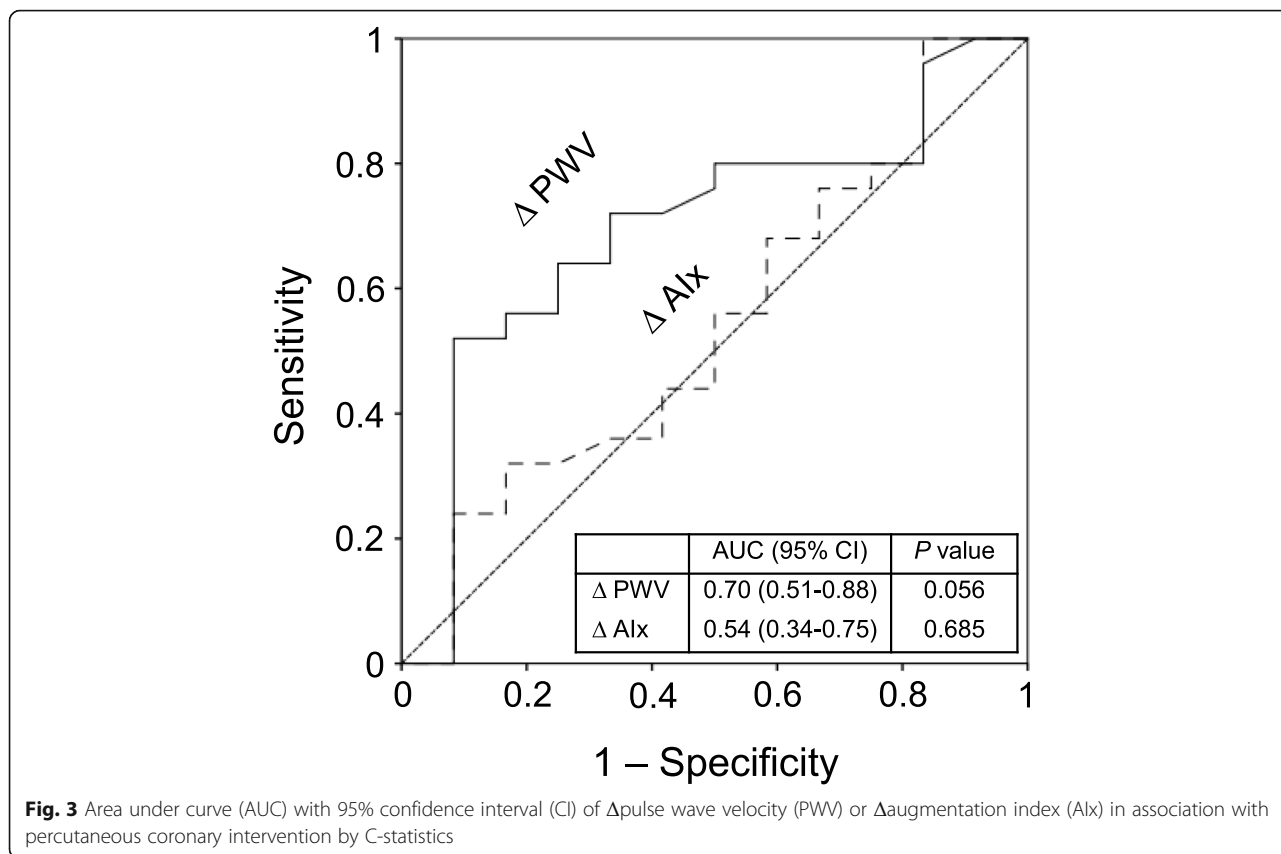
Values are mean ± standard

AIX Augmentation index, BP Blood pressure

CAD. In this clinical setting, simple PWV value may not differentiate patients with CAD and the lesion severity of CAD. In the previous study, we showed that PWV value at rest was not different between patients with and without CAD, but after 3-min handgrip exercise, PWV was significantly increased only in patients with CAD [24]. However, the change of PWV after handgrip exercise showed a diverse pattern such that PWV increased even in patients without CAD, and a cut-off point of

$\Delta$ PWV after handgrip exercise, which was associated with the lesion extent of CAD and the necessity for coronary revascularization, was not evaluated in the previous study. In this study, higher  $\Delta$ PWV group had more 2- or 3-vessel CAD and underwent more PCI than lower  $\Delta$ PWV group. On the other hand, the lesion extent of CAD and the necessity for PCI were not different between higher and lower  $\Delta$ AIX groups. In addition, C-statistics and multiple logistic regression analysis showed





**Fig. 3** Area under curve (AUC) with 95% confidence interval (CI) of  $\Delta$ pulse wave velocity (PWV) or  $\Delta$ augmentation index (AIx) in association with percutaneous coronary intervention by C-statistics

that  $\Delta$ PWV was associated with PCI but not  $\Delta$ AIx. These findings suggest that  $\Delta$ PWV may be used as an index for differentiating the lesion extent of CAD and the necessity for coronary revascularization even in elderly patients with hypertension, but  $\Delta$ AIx may not.

This study has several limitations. First, a fluid-filled catheter system, instead of a high-fidelity micromanometer, was used to record the pressure waveforms. A definite merging point of the forward and the reflected waves on the recorded pressure waveform was not identified in aortic pressure waveforms of 4 patients (9.5%). Second, over half of patients were taking medications with a vasodilation property, which may influence the change of BP, PWV, and AIx after handgrip exercise. However such medications were equally taken in both higher and lower  $\Delta$ PWV or  $\Delta$ AIx groups, and baseline central and peripheral BP were not different between groups. Third, PCI performed not only on the day of the study but also 1 year ago was counted as having coronary revascularization. Including only prospectively conducted coronary revascularization would have increased the feasibility of the study. Fourth, the number of patients might not be enough to accurately evaluate the changes of PWV and AIx after handgrip exercise. Nevertheless, the association between higher  $\Delta$ PWV and the

lesion extent of CAD or the necessity for PCI was demonstrated.

This was an invasive study that measured hemodynamic parameters during CAG. To be widely use, the applicability of a non-invasive method measuring  $\Delta$ PWV or  $\Delta$ AIx after handgrip exercise using an applanation tonometry needs to be validated in a future study.

**Conclusions**

Both PWV and AIx increased after isometric handgrip exercise, and  $\Delta$ PWV was significantly correlated with  $\Delta$ AIx. However, higher  $\Delta$ PWV was associated with the lesion extent of coronary atherosclerosis and the necessity for coronary revascularization, but higher  $\Delta$ AIx was not.

**Abbreviations**

AIx: Augmentation index; AP: Augmentation pressure; CAD: Coronary artery disease; CAG: Coronary angiography; PCI: Percutaneous coronary intervention; PWV: Pulse wave velocity; RAS: Renin-angiotensin system

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### Authors' contributions

SK and SJ conceived of this study, participated in its design and coordination, analyzing data, and writing a draft of this manuscript. YK, JB, and KB participated in obtaining written informed consents from patients, obtaining waveforms, and data analysis. JL, JC, and SK, participated in data analysis, and helped to conduct the literature review and draft the manuscript. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Jeju National University Hospital (IRB 2011–19). Written informed consents were obtained from participating patients or legal representative.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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