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Augmentation Index Does Not Reflect Risk of Coronary Artery Disease in Elderly Patients

Shuji Hayashi, MD; Hirotsugu Yamada, MD, PhD; Mika Bando, MD; Junko Hotchi, MD, PhD; Takayuki Ise, MD, PhD; Koji Yamaguchi, MD, PhD; Takashi Iwase, MD, PhD; Takeshi Soeki, MD, PhD; Tetsuzo Wakatsuki, MD, PhD; Toshiaki Tamaki, MD, PhD; Masataka Sata, MD, PhD

Background: Augmentation index (AI) has been used as a clinical index of arterial stiffness and has been reported to be an independent predictor of cardiovascular events, but some investigators have reported that AI is not a useful marker to identify coronary artery disease (CAD) in elderly patients. The majority of CAD patients are elderly people, therefore the aim of this study was to examine whether AI is a useful marker to identify the risk of CAD.

Methods and Results: A total of 120 patients (69±10 years of age; 83 male) who underwent cardiac catheterization for suspected CAD were enrolled. Invasive central blood pressure (BP) was measured using a fluid-filled catheter. Non-invasive AI was calculated by the SphygmoCor (AtCor Medical) system at the end of catheterization. Subjects consisted of 99 patients with CAD and 21 patients without CAD. There was no significant difference in AI between the CAD and the non-CAD groups (24±10 vs. 24±14%). Non-invasive systolic central BP was lower than the invasive systolic central BP (115±18 vs. 130±23 mmHg, P<0.001) in all patients. Non-invasive diastolic central BP was greater than the invasive diastolic central BP (67±10 vs. 63±10 mmHg, P<0.001).

Conclusions: In elderly patients, AI may not be a useful marker to identify CAD. (*Circ J* 2014; **78:** 1176–1182)

Key Words: Arterial stiffness; Augmentation index; Central blood pressure; Coronary artery disease

The guidelines on arterial hypertension from the European Society of Hypertension and the European Society of Cardiology describe the importance of conducting blood pressure (BP) management using clinical markers for arterial stiffness.[1] Among them, augmentation index (AI) of central BP has been widely used as a clinical index of arterial stiffness.[2–4] AI is defined as the percentage of the central pulse pressure attributed to enhancement (augmentation) due to the reflected pulse wave. Karamanoglu et al developed a generalized transfer function to estimate the central BP waveform from the radial arterial pressure waveform.[5] In addition, they developed a device for non-invasively estimating the central BP from the radial arterial pulse wave (SphygmoCor®). In their system, the central BP is calculated from the radial artery pressure, which is estimated from the radial artery pulse waveform obtained using a tonometer (pressure sensor) as well as brachial BP measured by the oscillometric method. Given that the SphygmoCor allows measurement of central BP and AI non-invasively, many investigators have used these indices, and additional devices for estimating central BP and AI have been developed in some countries. There are currently 2 main systems used for measuring AI: the SphygmoCor system (AtCor Medical, Australia) and the HEM-9000AI system (Omron Healthcare, Japan). The SphygmoCor can calculate aortic AI, whereas the HEM-9000AI can analyze radial AI. It was reported that radial AI correlated well with aortic AI.[6] On the basis of the evidence obtained from previous studies using these devices, recommendations on the clinical usefulness of AI and central BP were included in the European Society of Cardiology Guidelines[1] and the American Heart Association's consensus document.[7]

According to the majority of reports referenced in those guidelines, it was suggested that indices obtained from the central BP including AI were strong independent predictors of cardiovascular events.[8–12] There were some reports, however, that indicated that AI was not useful for predicting outcome in some subjects >60 years old or who had severe atherosclerosis (eg, patients undergoing chronic dialysis for kidney disease).[13,14] Of the articles that describe the usefulness of AI, Hayashi et al and Weber et al indicated that AI is a useful risk marker for coronary artery disease (CAD).[8,10] In contrast, Cho et al recently reported that AI is not a useful marker to identify CAD in subjects

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Ultrasound Examination Center (S.H.), Department of Cardiovascular Medicine (H.Y., M.B., J.H., T. Ise, K.Y., T. Iwase, T.S., T.W., M.S.), Tokushima University Hospital, Tokushima; and Department of Pharmacology, Institute of Health Biosciences, University of Tokushima Graduate School, Tokushima (T.T.), Japan

Mailing address: Hirotsugu Yamada, MD, PhD, Department of Cardiovascular Medicine, Tokushima University Hospital, 2-50-1 Kuramoto-cho, Tokushima 770-8503, Japan. E-mail: yamadah@tokushima-u.ac.jp

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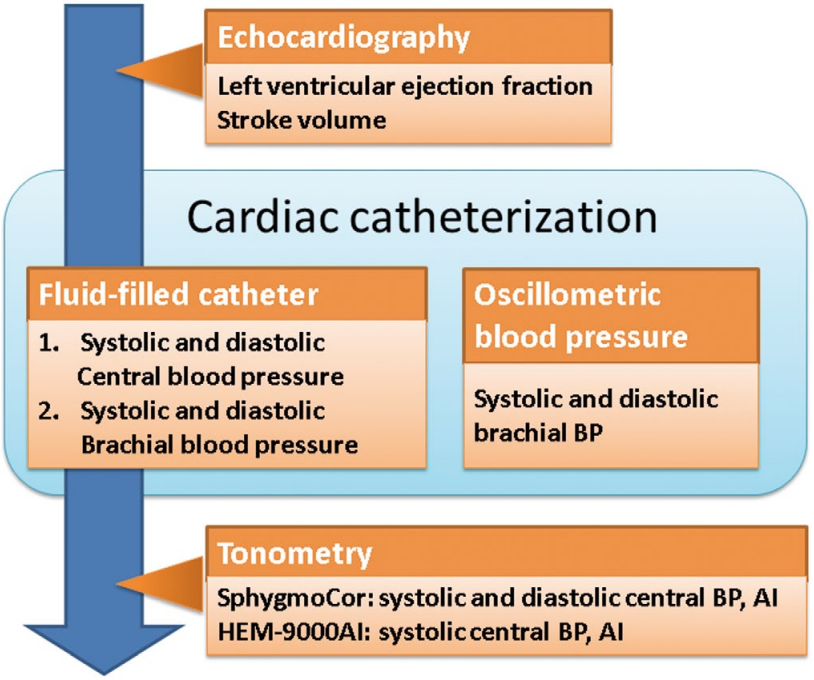

Figure 1. Flowchart of study protocol. In order to check for exclusions, echocardiography was done before cardiac catheterization. At the end of cardiac catheterization, invasive central and brachial pressure were measured. Oscillometric blood pressure (BP) was obtained simultaneously. Immediately after the catheterization, non-invasive central BP was measured using tonometry. AI, augmentation index.

aged >65.[15] In fact, Weber et al reported that significant difference in AI between the CAD and non-CAD group was found in patients up to 60 years of age (17.2±9.4 vs. 11.7±10.3%, P=0.002), whereas no significant difference was found in patients older than 60 years (16.7±10.2 vs. 18.1±10.1%, P=0.61).[10] In routine medical practice, the target age group for the assessment of the risk of CAD is >60 years of age. Therefore, we examined whether AI is a useful marker to identify the risk of CAD in the real world, including in elderly patients.

Methods

Subjects

The present subjects consisted of 120 patients undergoing cardiac catheterization at Department of Cardiovascular Medicine, Tokushima University Hospital between February 2012 and September 2012. All patients gave written informed consent. Patients with moderate or severe mitral valve disease, moderate or severe aortic valve disease and left ventricular outflow tract obstruction were excluded. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or use of antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl or ≥200 mg/dl at 2 hours after glucose load or HbA1C ≥6.5% or treatment with anti-hyperglycemic agents. Dyslipidemia was defined as serum concentration of triglycerides, total cholesterol, or low-density lipoprotein cholesterol ≥150 mg/dl, 220 mg/dl or 140 mg/dl, respectively, or a serum high-density lipoprotein cholesterol concentration <40 mg/dl or anti-hyperlipidemic drug treatment. Chronic renal failure was defined as glomerular filtration rate <60 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$.

Study Protocol

Figure 1 shows the study protocol and parameters that were measured. Routine echocardiography was performed before cardiac catheterization in order to check the exclusions. We measured left ventricular ejection fraction (LVEF) and stroke volume from 2-D echocardiography according to standard guidelines.[16] At the end of cardiac catheterization, invasive central BP was measured in the ascending aorta using a fluid-filled catheter system. BP was invasively measured while monitoring the impact of intra-circuit resonance, attenuation and air bubbles.[17,18] The natural frequency of the present system was >20 Hz and the damping coefficient was ≥0.3. We inserted a 5- or 6-Fr sheath (Introducer II; Terumo Medical, Tokyo, Japan) and a 5- or 6-Fr catheter into the radial or brachial artery. The length from the transducer to the catheter tip was <1.5 meters. An electrical filter was inserted into the amplifier. The transducer was kept at the mid-axillary line level during examination and zero calibrated to the atmosphere before catheterization. Central BP was measured at the ascending aorta, checking on fluoroscopy. The BP was recorded and analyzed using a clinical polygraph (RMC-3100; Nihon Koden, Tokyo, Japan). BP was invasively measured during catheterization and recorded using the RMC-3100. The brachial artery pressure was also measured with the same system to investigate the accuracy of measuring non-invasive brachial artery pressure in 55 subjects. Oscillometric BP was obtained simultaneously. Immediately after catheterization, non-invasive central BP was measured using the SphygmoCor system. The systolic, diastolic central BP and AI were obtained using this system. Systolic central BP and AI were also obtained with the HEM-9000AI system in 16 subjects. Coronary angiography was performed by standard techniques, and subjects were divided into 2 groups according to the results. A total of 99 patients had ≥75% stenosis according to the American Heart Association classification in at least 1 branch of a coronary artery[19] and were categorized into the CAD group; the other 21 were classified into the non-CAD group. This study protocol was approved by the ethics committee of Tokushima University Hospital (Tokushima, Japan).

Table 1. Patient Background

	Overall (n=120)	CAD (n=99)	Non-CAD (n=21)	P-value
Age (years)	69±10	67±14	70±9	0.301
Gender	83 (69.1)	72 (72.7)	11 (52.3)	0.068
Body height (cm)	159.7±8.9	159.4±9.8	159.8±8.7	0.861
Body mass index (kg/m²)	23.7±3.6	23.1±4.0	23.9±3.5	0.335
SBP (mmHg)	125±19	130±15	124.3±20	0.158
DBP (mmHg)	66±10	67±10	65±11	0.567
Pulse rate (beats/min)	63±9	65±9	63±10	0.408
LVEF (%)	60.2±10.4	61.6±9.4	60.0±10.6	0.522
Stroke volume (ml)	52.0±14.2	51.9±14.2	52.0±13.3	0.976
Background disease				
Hypertension	85 (70.8)	71 (71.7)	14 (66.7)	0.647
Diabetes	48 (40.0)	40 (40.4)	8 (38.1)	0.846
Dyslipidemia	87 (72.5)	80 (80.8)	7 (33.3)	<0.001
Chronic renal failure	53 (44.2)	48 (48.5)	5 (23.8)	0.039
Medication	98 (81.7)	83 (83.8)	15 (71.4)	0.185
ACEI	22 (18.3)	20 (20.2)	2 (9.5)	0.175
ARB	47 (39.2)	37 (37.4)	10 (47.6)	0.387
β-blockers	43 (35.8)	39 (39.4)	4 (19.0)	0.079
Calcium channel blockers	45 (37.5)	34 (34.3)	11 (52.3)	0.123
Nitrates	19 (0.8)	17 (17.2)	2 (9.5)	0.387
Diuretics	15 (12.5)	14 (14.1)	1 (4.8)	0.241

Data given as mean±SD or n (%).
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CAD, coronary artery disease; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Table 2. Comparisons of Various BPs and AI Between CAD and Non-CAD Groups

	Overall (n=120)	CAD (n=99)	Non-CAD (n=21)	P-value
Non-invasive method (SphygmoCor)				
Systolic central BP (mmHg)	115±18	114±18	119±16	0.251
Diastolic central BP (mmHg)	67±10	66±10	67±9	0.542
AI (%)	23.9±11.0	23.9±10.3	23.9±14.1	0.990
Invasive method (cardiac catheterization)				
Systolic central BP (mmHg)	130±23	130±23	130±24	0.886
Diastolic central BP (mmHg)	63±10	62±10	68±9	0.020

Data given as mean±SD.
AI, augmentation index; BP, blood pressure. Other abbreviation as in Table 1.

Statistical Analysis

Data analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). All results are expressed as mean±SD unless otherwise specified. Comparison of continuous parameters between the CAD and non-CAD groups was done using unpaired Student's t-test or Mann-Whitney test. The gender difference in the CAD and non-CAD group was analyzed using Mann-Whitney test. Categorical variables were compared using the chi-squared test. In addition, As a post-hoc analysis of statistical power, we calculated the effective dose (d) and statistical power (1-β) using G*Power 3.1[20] in accordance with Cohen.[21] Pearson's correlation analysis, paired Student's t-test and Bland-Altman plots were used to assess the agreement between the non-invasive and invasive BP measurements. P<0.05 was considered statistically significant.

Results

Subject Characteristics

The subjects consisted of 85 patients (70.8%) with hypertension, 48 patients (40.0%) with diabetes mellitus, 87 patients (72.5%) with dyslipidemia, and 99 patients (82.5%) with CAD (Table 1). There were no significant differences between the CAD and non-CAD groups in age, gender, body mass index, non-invasive brachial BP, pulse rate, LVEF or stroke volume. The prevalence of hypertension and diabetes did not differ between the 2 groups, whereas the prevalence of chronic renal failure and dyslipidemia was higher in the CAD group than in the non-CAD group, but there was no significant difference in the use of antihypertensive drugs between the 2 groups.

Central BP and AI in CAD

The invasive systolic central BP was similar between the CAD and non-CAD groups (130±23 vs. 130±24 mmHg, P=0.886),

whereas the invasive diastolic central BP in the CAD group was significantly lower than that in the non-CAD group (62±10 vs. 68±9 mmHg, P=0.020). Invasive central pulse pressure in the CAD group was 5 mmHg higher than in the non-CAD group (67±22 vs. 63±21 mmHg), but there were no significant differences between the 2 groups in the non-invasive systolic central BP as well as the non-invasive diastolic central BP (Table 2).

Mean AI was 24±10% in the CAD group and 24±14% in the non-CAD group; there was no significant difference between the 2 groups, and both values were within the normal range for age (Table 1). On comparing AI between the CAD group and the non-CAD group using t-test, the effective dose was d=0.003 and the statistical power was 1-β=0.05.

Both the CAD group and non-CAD group were divided according to gender and compared. No significant difference was found in age (P=0.850), height (P=0.262), heart rate (P=0.111) or rate of medication intake (P=0.924) between men in the CAD group and non-CAD group. In men, no significant difference in AI was found between the CAD group and the non-CAD group (23.2±10.8% vs. 17.6±12.6%, P=0.181). Women in both the CAD group and non-CAD also had no significant difference in age (P=0.767), height (P=0.514), heart rate (P=0.368) or rate of medication intake (P=0.084). As with men, there was no significant difference in AI observed in women between the CAD group and non-CAD group (25.7±8.4% vs. 30.8±12.8%, P=0.263).

In addition, as shown in Figure 2, SphygmoCor's radial AI and Omron's radial AI were closely correlated.

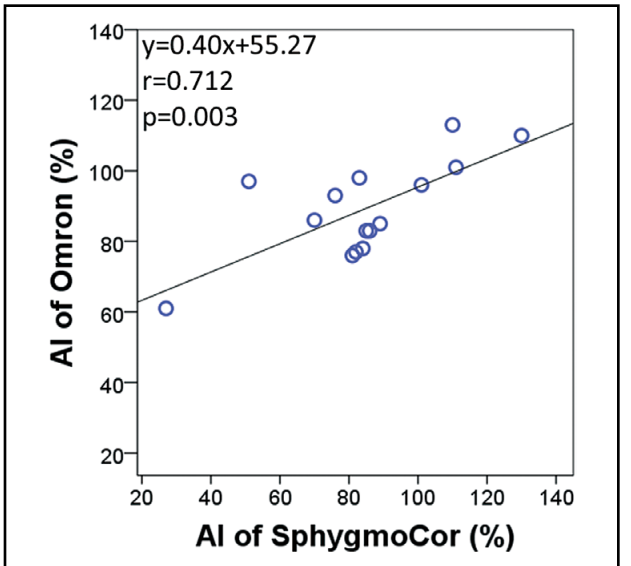

Figure 2. Relationship between augmentation index (AI) in the radial artery determined using the SphygmoCor device and that measured using the HEM-9000AI (Omron) device.

Non-Invasive and Invasive Central BP Measurements

The non-invasive systolic central BP estimated with SphygmoCor was closely correlated with catheter measurement in the ascending aorta (r=0.765, P<0.001; Figure 3). SphygmoCor, however, underestimated the invasive systolic central BP with an average difference of −15 mmHg (95% confidence interval [CI]: −17 to −12 mmHg, P<0.001; Table 3; Figure 4). Omron overestimated systolic central BP with an average difference of +11 mmHg (95% CI: 0–22 mmHg, P=0.045). Although the non-invasive diastolic central BP estimated with SphygmoCor was closely correlated with the catheter measurement in the ascending aorta (r=0.668, P<0.001; Figure 3), SphygmoCor overestimated the diastolic central BP with an average difference of 4 mmHg (95% CI: 2–5 mmHg, P<0.001; Table 3; Figure 4). Because the Omron device does not provide diastolic central BP estimation, we compared only the non-invasive estimations of diastolic and pulse pressures measured on the SphygmoCor device with the invasive catheter measurements. Non-invasive systolic brachial BP underestimated invasive systolic pressure

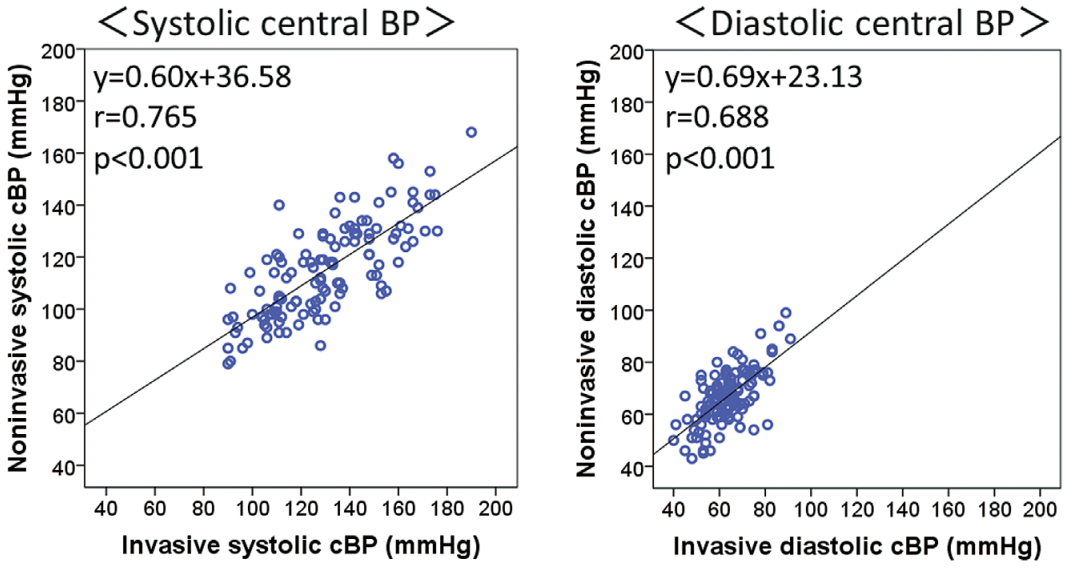

Figure 3. Relationship between non-invasive central blood pressure (cBP) measured using SphygmoCor and invasive cBP measured with a catheter.

Table 3. Comparisons of Various BPs Between Non-Invasive and Invasive Methods

	Non-invasive	Invasive (catheter)	Difference from the catheter (95% CI)	P-value
SphygmoCor (n=120)				
Systolic central BP (mmHg)	115±18	130±23	−15 (−17 to −12)	<0.001
Diastolic central BP (mmHg)	67±10	63±10	4 (2–5)	<0.001
Omron (n=16)				
Systolic central BP (mmHg)	138±22	127±26	11 (0–22)	0.043
Brachial pressure (n=55)				
Systolic central BP (mmHg)	137±24	138±25	−2 (−3 to 0)	<0.001
Diastolic central BP (mmHg)	68±11	63±11	5 (3–7)	<0.001

Data given as mean±SD.
CI, confidence interval. Other abbreviation as in Table 2.

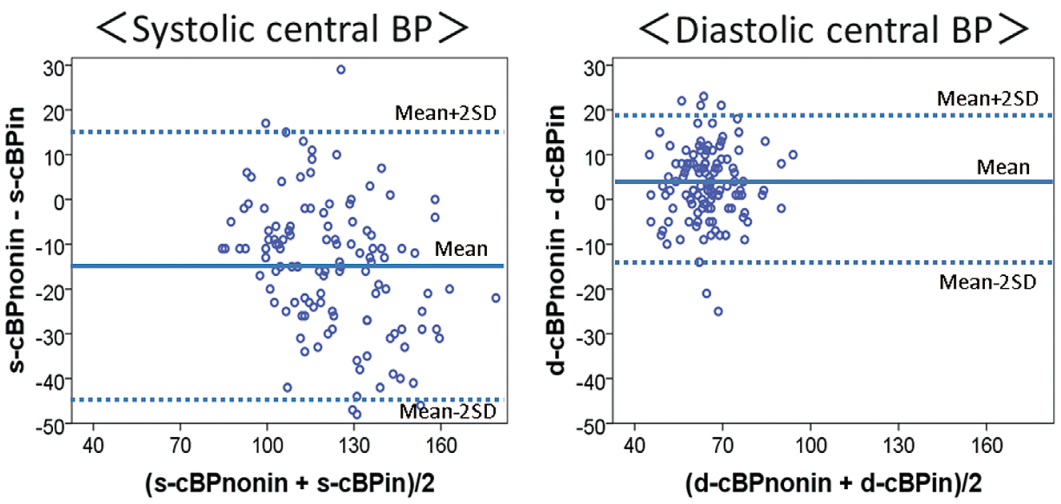

Figure 4. Bland-Altman plots for comparison of non-invasive central blood pressure ($cBP_{non\text{-}inv}$) measured with the SphygmoCor device (systolic and diastolic, $s\text{-}cBP_{non\text{-}inv}$, $d\text{-}cBP_{non\text{-}inv}$, respectively) against invasive central blood pressure with a catheter (systolic and diastolic, $s\text{-}cBP_{inv}$, $d\text{-}cBP_{inv}$, respectively). The 95% confidence intervals are given as ±2 SD of the difference.

with an average difference of −2 mmHg (95% CI: −3 to 0 mmHg, P<0.001). Non-invasive diastolic brachial BP overestimated invasive diastolic pressure with an average difference of 5 mmHg (95% CI: 3–7 mmHg, P<0.001; Table 3).

Discussion

In the present study, AI obtained with SphygmoCor did not increase in patients with CAD. Invasive diastolic central BP in the CAD group was significantly lower than that in the non-CAD group by 5 mmHg, which indicates that arterial stiffness was increased in CAD.[2,22,23] But AI did not reflect this augmented arterial stiffness in the present subjects. Because there are few previous reports that examined central BP and AI in relatively elderly patients with atherosclerosis,[12,24] this is a relatively large study to show that AI measured non-invasively is not a good index of arterial stiffness, especially in elderly patients who have greater cardiovascular risk. In addition, among studies examining the validation of non-invasively obtained central BP by applanation tonometry,[25] the present study has the highest number of subjects.

Effect of Aging on AI

Many investigators have shown that AI is a clinically useful index for predicting cardiovascular events,[8,10–12] but most of the subjects in those studies were younger than 65 years old and had mild–moderate atherosclerosis.[8,10,11] There are some reports showing that AI is not a useful marker to identify CAD in elderly patients (>60 years[13] or ≥65 years[15]). AI actually is known to increase with age before approximately 60 years and plateaus after that.[26–28] In the present study, the mean subject age was 69±10 years, which may be an important reason why AI was not influenced by CAD.

Other Factors Affecting AI

There are various factors that affect AI, including age, gender, height, heart rate and type of antihypertensive drugs.[6,29,30] These factors, however, were similar between the present CAD and non-CAD groups. The pressure sensor was placed on the artery, partially flattening (applanation) the arterial wall. With a balance between the internal and external arterial pressure, changes in BP were non-invasively measured.[31] Thus, when atherosclerosis is severe, sufficient flattening of the vascular wall may not be possible, resulting in inaccurate BP measurement by the

pressure sensor.

Correlation With Central BP

Non-invasive central BP measured with SphygmoCor did not agree well with the central BP obtained on cardiac catheterization. These same results were found in several previous studies in a small number of subjects.[32,33] Those studies showed that SphygmoCor underestimated systolic central BP and overestimated diastolic central BP. One study found that the accuracy of the non-invasive measurements of central BP depends on the accuracy of the measurement of brachial BP.[34] Several studies also showed that mean pressure did not always match due to various problems with fluid-filled catheter systems and oscillometric methods.[18,35,36] Historically, it is well known that non-invasive systolic BP tends to be lower than invasive systolic BP, and non-invasive diastolic BP tends to be higher than invasive diastolic BP.[37,38] The SphygmoCor system was originally designed to estimate central BP by means of invasive radial artery BP, although most users measure brachial BP using a cuff rather than invasive radial artery BP. This may be the factor that led to a lower than expected AI in elderly subjects. The algorithm for estimating central BP should be revised using the oscillometric measurement of central BP.

Study Limitations

First, the present subjects were scheduled for coronary angiography and had coronary risk factors; thus, the subjects even in the non-CAD group were not healthy. The prevalence of chronic renal failure and hyperlipidemia in the non-CAD group, however, was significantly lower than that in the CAD group. Furthermore, diastolic central BP in the non-CAD group was significantly lower than that in the CAD group, despite the lack of significant difference in systolic central BP between the 2 groups. Therefore, the non-CAD group served as an adequate control group with relatively normal arterial stiffness.

Second, measurements of invasive and non-invasive central BP were not completely simultaneous in the present study. In order to estimate central BP with the SphygmoCor and Omron systems, brachial BP measured using the oscillometric method is needed before measuring the pulse wave form from the radial artery by tonometry; thus simultaneous measurement of the central BP by tonometry and catheterization is not possible with either system.

Third, given that it was difficult to identify the incident pressure wave and the reflected wave in the central BP recording using the fluid-filled catheter system, we could not obtain the invasive AI in this study. In order to obtain the AI from invasive pressure recording, high-fidelity pressure measurement of central BP by catheter-tip manometer is required. Thus, direct comparison of invasive and non-invasive AI was not done.

Conclusions

We measured AI and central BP non-invasively using the SphygmoCor system in relatively elderly patients and found no difference in AI between patients with and without CAD. In elderly patients, AI may not be a useful marker to identify CAD.

Acknowledgments

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