ORIGINAL ARTICLE

Impact of the augmentation time ratio on direct measurement of central aortic pressure in the presence of coronary artery disease

Atsushi Mizuno¹, Katsumi Miyauchi², Yuji Nishizaki², Masahiro Yamazoe¹, Ikki Komatsu¹, Taku Asano¹, Hirotsugu Mitsuhashi¹, Yutaro Nishi¹, Koichiro Niwa¹ and Hiroyuki Daida²

The augmentation index measured by using the central artery pressure is associated with an increased risk of coronary artery disease (CAD). However, no study has examined the role of the time duration of the central artery pressure on CAD. Therefore, we evaluated the relationship between the central blood pressure time duration and the presence of CAD. All patients without a history of revascularization or prior myocardial infarction who underwent an elective coronary angiography at one of the two hospitals from January to September 2013 were analyzed. CAD was defined as a significant stenosis in one of the main coronary branches. The augmentation time ratio was defined as the ratio of the reflection to peak systolic time T2T1 duration divided by the peak systolic time to aortic notch T3T2 duration. We analyzed the relationship between the central pressure waveform (not only augmentation pressure) and the presence of CAD. A total of 146 (57.3%) out of 255 patients had a significant CAD. T2T1 duration was longer in the CAD group than the no CAD group, and the T3T2 duration was shorter in the CAD group than the no CAD group. The augmentation time ratio (T2T1/T3T2) was significantly larger in the CAD group than in the no CAD group. The augmentation index and augmentation pressure were lower in the no CAD group, but this difference was not statistically significant. The augmentation time ratio was an independent factor related to no CAD, especially in patients with a high augmentation index (odds ratio, 2.17; 95% confidence interval, 1.02–4.63). The augmentation time ratio was an independent factor related to the presence of CAD.

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Keywords: augmentation index (AI); augmentation time ratio; central artery pressure; coronary artery disease (CAD)

INTRODUCTION

Central aortic pressures are pathophysiologically more relevant than peripheral artery pressures when considering the pathogenesis of cardiovascular disease.^{1–3} Furthermore, central hemodynamic variables, such as augmentation index (AI), are independent predictors of cardiovascular events and mortality.^{3–8} Recent advances in noninvasive instrumentation to estimate central aortic pressure have allowed for estimation of the AI in many patients. A higher augmentation pressure and index measured by using the central artery pressure are associated with an increased risk of coronary artery disease (CAD).⁹ However, the lack of an established absolute cut-off value and its limited importance in males are known problems associated with the use of the AI.³

Although studies have investigated the amplification of central arterial pressure, time duration analysis of central arterial pressure has not been fully evaluated. Under these circumstances, direct central artery pressure waveform analysis is important, but it has not been fully studied. Therefore, the present study evaluated the

relationship between the central artery pressure waveform and presence of CAD.

METHODS

Study design

This multicenter prospective cross-sectional study was performed at St. Luke's International Hospital and Juntendo University Hospital located in the center of Tokyo, Japan. We collected clinical data, performed central blood pressure wave analysis, and recorded coronary angiography results. This study was approved by the Institutional Ethics Committee of each hospital, and all subjects gave informed consent.

Patient enrollment

We enrolled consecutive patients who underwent a scheduled coronary angiography and central pressure recordings from January to September 2013. Three patients were excluded because of inadequate coronary angiographic information. In this study, we included other coronary angiography patients, and the exclusion criteria were as follows: previous percutaneous coronary intervention; coronary artery bypass grafting or myocardial infarction; and patients whose central pressure measurements were not available.

¹Department of Cardiology, St Luke's International Hospital, Tokyo, Japan and ²Department of Cardiology, Juntendo University Graduate School of Medicine, Tokyo, Japan
Correspondence: Dr A Mizuno, Department of Cardiology, St Luke's International Hospital 9-1, Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan.
E-mail: atmizu@luke.ac.jp

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Coronary angiography

Coronary angiography was performed via the radial, brachial or femoral artery by using 4-Fr or 5-Fr Judkins right and left diagnostic coronary angiography catheters. We recorded the central arterial pressure in the ascending aorta at the

Figure 1 Pressure waveform measurement points. P0, diastolic pressure; P1, reflection pressure; P2, peak systolic pressure; P3, dicrotic notch pressure (incisura). T0–T3 was measured from the Q wave. Augmentation time ratio is defined as T2/T1 duration divided by T3/T2 duration. ET, ejection time; PEP, pre-ejection period. A full color version of this figure is available at the *Hypertension Research* journal online.

end of the expiratory phase using a saline-filled catheter attached to a pressure sensor.¹⁰ The coronary arteries were classified according to a modified American College of Cardiology/American Heart Association classification.¹¹ All coronary angiograms were visually assessed by at least two experienced angiographers (each angiography performer), and a consensus was reached. The angiographers were blinded to the results of central pressure analysis. Significant narrowing was defined as either $\geq 70\%$ reduction in the internal diameter of the right coronary artery, left anterior descending or left circumflex coronary artery or $\geq 50\%$ reduction in the internal luminal diameter of the left main coronary artery.¹² No CAD was defined as the absence of significant narrowing in the coronary arteries observed on the coronary angiogram.

Central artery pressure analysis

The recordings were obtained at a paper speed of 100 mm s^{-1} . Central artery pressure waveform analysis was performed on printed paper by two blinded, experienced cardiology doctors (AM and YN). We measured four point pressures and time intervals similar to previous studies (Figure 1) (P0, diastolic pressure; P1, reflection pressure; P2, peak systolic pressure; P3, dicrotic notch pressure (incisura)).² The reflection pressure (P2) was carefully defined determined at the first systolic inflection point of the central artery pressure waveform.¹³ Augmentation pressure was defined by differences between P1 and P2, and AI was calculated by augmentation pressure divided by pulse pressure (P2–P0). We also calculated the time length, such as the T1/T0 duration as shown in Figure 1. Time points such as T0, T1, T2 and T3 were determined corresponding to the four measure points according to the P0, P1, P2 and P3, respectively. The augmentation time ratio was defined as T2/T1 duration divided by T3/T2 duration. Each interval was corrected for the RR interval, and the AI was normalized to a heart rate of 75 b.p.m. (AIx@75).^{9,14} We compared these

Table 1 Baseline characteristics

	Total (n = 255)	Coronary artery disease: no (n = 109)	Coronary artery disease: yes (n = 146)	P-value
Age (years) $\pm$ s.d.	67.0 $\pm$ 12.2	67.4 $\pm$ 12.8	66.7 $\pm$ 11.8	0.674
Male gender, n (%)	193 (75.7)	67 (61.5)	126 (86.3)	<0.001*
Height, cm	163.9 $\pm$ 9.2	161.6 $\pm$ 9.8	165.5 $\pm$ 8.4	<0.001*
Smoking, n (%)	93 (36.5)	39 (35.8)	54 (37)	0.896
Family history, n (%)	15 (5.9)	4 (3.7)	11 (7.6)	0.283
Diabetes mellitus, n (%)	83 (32.5)	27 (24.8)	56 (38.4)	0.03*
Hypertension, n (%)	198 (77.6)	80 (73.4)	118 (80.8)	0.174
Dyslipidemia, n (%)	157 (61.6)	59 (54.1)	98 (67.1)	0.038*
Hyperuricemia, n (%)	46 (18)	21 (19.3)	25 (17.1)	0.742
Atrial fibrillation, n (%)	23 (9)	12 (11)	11 (7.5)	0.381
Chronic kidney disease (eGFR $< 60 \text{ ml min}^{-1}$), n (%)	72 (28.2)	33 (30.3)	39 (26.7)	0.575
Hemodialysis, n (%)	12 (4.7)	6 (5.5)	6 (4.1)	0.767
Medications				
ACE-I, n (%)	21 (8.2)	7 (6.4)	14 (9.6)	0.491
ARB, n (%)	93 (36.5)	44 (40.4)	49 (33.6)	0.294
Beta-blocker, n (%)	80 (31.4)	33 (30.3)	47 (32.2)	0.786
Calcium channel blocker, n (%)	75 (29.4)	29 (26.6)	46 (31.5)	0.409
Statin, n (%)	105 (41.2)	31 (28.4)	74 (50.7)	<0.001*
Laboratory data				
Total cholesterol (mg dl^{-1}) $\pm$ s.d.	179 $\pm$ 34.7	182.7 $\pm$ 36.8	176 $\pm$ 32.9	0.276
Low-density lipoprotein cholesterol (mg dl^{-1}) $\pm$ s.d.	103.9 $\pm$ 30.8	101.6 $\pm$ 31.7	105.6 $\pm$ 30.2	0.398
High-density lipoprotein cholesterol (mg dl^{-1}) $\pm$ s.d.	50.8 $\pm$ 15.7	54.7 $\pm$ 18	48 $\pm$ 13.3	0.003*
Triglycerides (mg dl^{-1}) $\pm$ s.d.	138.8 $\pm$ 105	119.6 $\pm$ 68.8	152.5 $\pm$ 123	0.016*
Hemoglobin A1c (%) $\pm$ s.d.	6.1 $\pm$ 1.2	6.0 $\pm$ 1.0	6.2 $\pm$ 1.3	0.202
Serum creatinine (mg dl^{-1}) $\pm$ s.d.	1.3 $\pm$ 2	1.3 $\pm$ 2.3	1.2 $\pm$ 1.7	0.751
eGFR (ml min^{-1}) $\pm$ s.d.	68.3 $\pm$ 27.4	68.8 $\pm$ 30.7	68 $\pm$ 24.8	0.258

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

*Indicates statistical significance.

Table 2 Waveform analysis

	Total (n = 255)	Coronary artery disease; no (n = 109)	Coronary artery disease; yes (n = 146)	P-value
<i>Time interval</i>				
T0; PEP (ms) $\pm$ s.d.	118.1 $\pm$ 34.8	119.9 $\pm$ 37.9	116.8 $\pm$ 32.5	0.479
T1 (ms) $\pm$ s.d.	223.4 $\pm$ 45.6	227.5 $\pm$ 48.3	220.3 $\pm$ 43.3	0.215
T2 (ms) $\pm$ s.d.	347.3 $\pm$ 49.2	345.9 $\pm$ 55	348.4 $\pm$ 44.5	0.700
T3 (ms) $\pm$ s.d.	455.2 $\pm$ 49.7	460.2 $\pm$ 52.6	451.4 $\pm$ 47.2	0.161
T1T0 duration (ms) $\pm$ s.d.	105.3 $\pm$ 23.8	107.6 $\pm$ 25.6	103.5 $\pm$ 22.2	0.181
T2T1 duration (ms) $\pm$ s.d.	124 $\pm$ 28.7	118.4 $\pm$ 30.4	128.1 $\pm$ 26.8	0.008*
T3T2 duration (ms) $\pm$ s.d.	107.9 $\pm$ 27.2	114.3 $\pm$ 28.8	103 $\pm$ 25	0.001*
T2T0 duration (ms) $\pm$ s.d.	229.2 $\pm$ 34.8	226 $\pm$ 40.5	231.6 $\pm$ 29.7	0.223
T3T0 duration; ET (ms) $\pm$ s.d.	337.1 $\pm$ 38.3	340.3 $\pm$ 42.9	334.7 $\pm$ 34.3	0.257
T3T1 duration (ms) $\pm$ s.d.	231.8 $\pm$ 33.1	232.8 $\pm$ 36.6	231.1 $\pm$ 30.3	0.702
PEP/ET	0.36 $\pm$ 0.12	0.36 $\pm$ 0.13	0.35 $\pm$ 0.1	0.621
Augmentation time ratio (T2T1/T3T2)	1.3 $\pm$ 0.6	1.1 $\pm$ 0.5	1.4 $\pm$ 0.6	0.001*
Augmentation pressure (mm Hg) $\pm$ s.d.	20.2 $\pm$ 12.5	20.2 $\pm$ 12.8	20.1 $\pm$ 12.2	0.961
Aix@75	0.31 $\pm$ 0.14	0.30 $\pm$ 0.13	0.31 $\pm$ 0.14	0.823
Heart rate (b.p.m.) $\pm$ s.d.	71.2 $\pm$ 12.7	70.4 $\pm$ 14	71.8 $\pm$ 11.7	0.413
P0 (mm Hg) $\pm$ s.d.	69.8 $\pm$ 13.5	68.1 $\pm$ 13.6	71 $\pm$ 13.4	0.090
P1 (mm Hg) $\pm$ s.d.	113.2 $\pm$ 20.4	112.3 $\pm$ 22.3	113.8 $\pm$ 19	0.554
P2 (mm Hg) $\pm$ s.d.	133.4 $\pm$ 25.2	132.5 $\pm$ 27.6	134 $\pm$ 23.4	0.649
P3 (mm Hg) $\pm$ s.d.	104.5 $\pm$ 18.3	102.3 $\pm$ 18.6	106.1 $\pm$ 17.9	0.105

Abbreviations: Aix, augmentation index; ET, ejection time; PEP, pre-ejection period.

*Indicates statistical significance.

Table 3 Risk factors for coronary artery disease in all patients (n=255)

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (years)	0.996	0.975–1.016	0.673	1.011	0.986–1.037	0.398
Male gender	3.949	2.147–7.264	<0.001	2.940	1.181–7.322	0.021*
Height	1.048	1.019–1.078	<0.001	1.012	0.967–1.06	0.596
Smoking	1.054	0.629–1.765	0.843			
Family history	2.155	0.667–6.961	0.199			
Diabetes mellitus	1.890	1.092–3.269	0.023	1.772	0.978–3.208	0.059
Hypertension	1.528	0.845–2.761	0.160			
Dyslipidemia	1.730	1.038–2.884	0.035	1.443	0.825–2.526	0.199
Hyperuricemia	0.866	0.456–1.645	0.660			
Atrial fibrillation	0.659	0.279–1.554	0.341			
Chronic kidney disease (eGFR <60 ml min ⁻¹)	0.839	0.485–1.453	0.532			
Hemodialysis	0.736	0.231–2.346	0.604			
Augmentation index	1.236	0.196–7.811	0.822	0.596	0.066–5.387	0.645
Augmentation time ratio (T2T1/T3T2)	2.324	1.363–3.964	0.002	2.234	1.185–4.214	0.013*

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

*Indicates statistical significance.

central artery pressure waveform variables according with the presence or absence of CAD.

Statistical analysis

Continuous data are expressed as the mean $\pm$ s.d., and comparisons between the groups were made by using the *t*-test or Mann–Whitney *U*-test. Categorical data were compared between the groups with the χ^2 - or Fisher's exact test. Statistical significance was inferred when *P* < 0.05. We analyzed the patients' variables and presence of CAD. A logistic regression analysis was performed, including variables with a *P*-value < 0.10 in a univariate analysis in addition to age, sex and AI. All statistical testing and data analysis were performed with SPSS (Statistical Package for the Social Sciences) version 17 (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 404 patients were enrolled. A total of 90, 29, 21 and 9 patients were excluded because of history of percutaneous coronary intervention, coronary artery bypass grafting, old myocardial infarction and poor central arterial pressure recording, respectively. A total of 255 patients were enrolled, and we compared 146 (57.3%) CAD patients with 109 (42.7%) no CAD patients. Table 1 shows the baseline patient characteristics for each group. The CAD group included more male patients and more patients with diabetes, dyslipidemia and history of statin use compared with the no CAD group.

Table 4 Risk factors for coronary artery disease in high AIx patients (n= 128)

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (years)	0.994	0.966–1.023	0.667	1.013	0.979–1.047	0.468
Male gender	2.486	1.122–5.509	0.025	1.946	0.524–7.220	0.32
Height	1.039	1.000–1.080	0.048	1.021	0.955–1.092	0.543
Smoking	0.845	0.404–1.767	0.654			
Family history	6.016	0.718–50.421	0.098	5.123	0.582–45.054	0.141
Diabetes mellitus	2.159	0.928–5.024	0.074	2.586	1.038–6.444	0.041*
Hypertension	1.372	0.579–3.253	0.473			
Dyslipidemia	1.516	0.741–3.103	0.255			
Hyperuricemia	1.133	0.49–2.622	0.770			
Atrial fibrillation	0.927	0.268–3.210	0.905			
Chronic kidney disease (eGFR <60 ml min ⁻¹)	0.812	0.379–1.739	0.592			
Hemodialysis	0.505	0.081–3.129	0.463			
Augmentation time ratio (T2T1/T3T2)	2.479	1.189–5.171	0.015	2.346	1.056–5.211	0.036*

Abbreviations: AIx, augmentation index; CI, confidence interval; eGFR, estimated glomerular filtration rate.

*Indicates statistical significance.

Table 5 Risk factors for coronary artery disease in low-AIx patients (n= 127)

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (years)	0.998	0.969–1.028	0.900	1.016	0.977–1.057	0.414
Male gender	7.437	2.737–20.214	<0.001	6.501	1.62–26.089	0.008*
Height	1.058	1.014–1.104	0.009	1.004	0.94–1.071	0.911
Smoking	1.290	0.624–2.669	0.492			
Family history	0.952	0.204–4.444	0.950			
Diabetes mellitus	1.704	0.816–3.561	0.156			
Hypertension	1.701	0.752–3.845	0.202			
Dyslipidemia	1.980	0.954–4.109	0.067	1.372	0.608–3.096	0.446
Hyperuricemia	0.593	0.212–1.653	0.317			
Atrial fibrillation	0.476	0.142–1.592	0.228			
Chronic kidney disease (eGFR <60 ml min ⁻¹)	0.875	0.396–1.935	0.742			
Hemodialysis	0.952	0.204–4.444	0.950			
Augmentation time ratio (T2T1/T3T2)	2.736	1.123–6.666	0.027	2.284	0.893–5.844	0.085

Abbreviations: AIx, augmentation index; CI, confidence interval; eGFR, estimated glomerular filtration rate.

*Indicates statistical significance.

Central artery pressure waveform analysis results

Table 2 shows the results of the central artery pressure waveform analysis. The T2T1 duration was shorter in the no CAD group than the CAD group, and T3T2 duration was longer in the no CAD group than the CAD group. The augmentation time ratio (T2T1/T3T2) was significantly lower in the no CAD group than the CAD group. P1 and P4 were significantly lower in the no CAD group than the CAD group. The AIx@75 and augmentation pressure was lower in the no CAD group than the CAD group, but this difference was not statistically significant.

Multivariate analysis showed that male gender and augmentation time ratio were independent variables for CAD (odds ratio (OR) 3.508, 95% confidence interval (CI); 1.842–6.679 and OR 2.217, 95% CI 1.179–4.169, respectively) (Table 3).

Patients were categorized into two groups according to the median AIx@75 (0.295), and variables that were independently associated with the presence of CAD were analyzed (Tables 4 and 5). The augmentation pressure and AI in the high- and low-AIx groups were 0.20 ± 0.06

vs. 0.41 ± 0.10 and 12.3 ± 6.2 mm Hg vs. 28.1 ± 12.1 mm Hg, respectively. In patients with a higher AIx@75, male gender (OR, 2.605; 95% CI, 1.075–6.312) and augmentation time ratio (OR, 2.339; 95% CI, 1.062–5.151) were independent variables. In patients with a lower AIx@75, male gender and augmentation time ratio were significant variables in the univariate analysis, but male gender was the only independent variable (OR, 6.489; 95% CI, 2.389–19.638).

DISCUSSION

We investigated the central artery pressure waveform in detail and showed the relationship between the augmentation time ratio and the presence of CAD.

Central artery pressure waveform analysis

Data regarding central artery pressure waveforms have already been published, and many previous reports showed that the augmentation pressure and AI were independent predictors of CAD and adverse outcomes.^{4,5,9} However, in our study, the augmentation time ratio

(but not AIx@75) was a significant independent predictor of the presence of CAD, which is different from results in previous studies. The reason why we could not show a relationship between AI and CAD might have been due to the differences in patient background compared with previous studies. First, the mean augmentation pressure serves as a predictive factor of the presence of CAD, especially in a group with a low augmentation pressure (7–8 mm Hg),⁶ whereas the mean augmentation pressure does not serve as a predictive factor in a group with a high augmentation pressure (12–14 mm Hg).¹⁵ The mean augmentation pressure in our study was 20 mm Hg, which was higher than previous studies. Second, the AI tends to be higher in males and patients with CAD.¹⁶ From this point of view, the previous study was limited, because they included only male patients with a high prevalence of CAD (406/465, 87.3%).¹⁰ In the current study, both males and females were included, and the prevalence of CAD was relatively lower (57.3%) than the previous study.

Augmentation time ratio

Central pressure augmentation is the sum of a forward running and a backward running or reflected pressure wave. The mechanism of this augmentation had been investigated previously. There are two different advocated mechanisms.¹⁷ The prevailing theory is that aortic stiffening leads to increased wave speed and amplitude of the reflected wave.¹⁸ The other mechanism is that aortic stiffening leads to an increase in the characteristic impedance of the proximal aorta, which means a proportional increase in the forward running pressure wave, if the cardiac output is maintained.¹⁹ Raymond *et al.*¹⁷ demonstrated that global stiffening augments systolic pressure principally through the increase in wave reflections, whereas local stiffening in the proximal aorta increases systolic pressure mainly through augmentation of the forward pressure wave. According to their theory, the augmentation time ratio is longer in the global arterial stiffening model than the local proximal aorta stiffening model, even if the augmentation pressure is equal in both models. This theory was one explanation for our study results: the augmentation time ratio rather than the AIx was related to the presence of CAD. Furthermore, females had an increased risk of stiffer large vessels comparing to males because of the genetic and hormonal influences, which could be assessed by the augmentation time ratio rather than the augmentation time index.²⁰ In females, some previous reports have questioned the value of the AI to predict cardiovascular disease.¹⁶ Twenty-five percent of the patients in our study were females, which might explain our results that the augmentation time ratio could predict CAD, but AIx could not.

Time duration analysis was also performed in the large clinical Conduit Artery Function Evaluation trial, but no study has investigated the association between cardiovascular disease and augmentation time ratio.² When we calculated the augmentation time ratio in the Conduit Artery Function Evaluation trial, the augmentation time ratio was apparently much longer in the atenolol group than the amlodipine group. This difference is one potential explanation for the higher events rate in the atenolol group compared with the amlodipine group.² Therefore, both the AIx and augmentation time ratio might predict poor outcomes more appropriately.

Limitations

This study has several limitations. First, the sample size was small. However, the current study explored the importance of time duration, and the main purpose of this study was to focus on central blood pressure amplitude (y axis, mm Hg) and time duration (x axis, ms). A large sample size study is necessary to reach reliable conclusions,

and we should assess the correlation between the augmentation time ratio and long-term clinical outcomes in a larger population. Second, the current study was observational in nature; therefore, even after adjustment, other unknown confounding factors might have affected the results.^{13,21} Third, we included atrial fibrillation patients, which might result in the lack of a relationship between AI (augmentation pressure) and CAD. However, because the augmentation time ratio was calculated by using several intervals in the systolic phase, we believe atrial fibrillation did not affect our conclusion.

CONCLUSION

The augmentation time ratio was an independent factor related to the presence of CAD.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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