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ORIGINAL ARTICLE

Central pulse pressure amplification is associated with more extensive and severe coronary artery disease

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Abstract

Objectives. We investigate the association between noninvasively determined central pulse waveform characteristics and the extent and severity of coronary artery disease (CAD) in patients undergoing coronary angiography with the clinical diagnosis of CAD. *Design.* We included 145 consecutive patients with stable angina pectoris (SAP), unstable angina pectoris (USAP), or acute myocardial infarction (AMI) who were decided to undergo coronary angiography. Gensini and SYNTAX scores were calculated. Noninvasive PWA was performed with the SphygmoCor system. *Results.* Dividing the patients into tertiles according to augmentation index (AIx), more patients had significant CAD with higher Gensini and SYNTAX scores and lower myocardial blush grade (MBG) ($p < 0.001$ for all) in the third tertile. The AIx value to predict the presence of moderate to severe CAD as determined by SYNTAX score ≥ 23 was 24.45% (ROC analysis AUC: 0.96; sensitivity 88%, specificity: 93%, 95% CI: 0.93–0.99, $p < 0.001$). AIx was significantly correlated with Gensini and SYNTAX scores in SAP, USAP, and AMI patients after adjusting for age, gender, height, heart rate, hypertension, and diabetes. *Conclusions.* Increased AIx is associated with the presence and severity of CAD, and it may be used in selected patients during cardiovascular evaluation in outpatient settings for risk stratification prior to coronary angiography.

Key words: *Augmentation index, pulse waveform analysis, extent and severity of coronary artery disease, SYNTAX score*

Introduction

The central aortic pressure wave is composed of a forward-traveling incident wave created by ventricular systole, and a subsequent reflected wave from the periphery. Increased aortic stiffness leads to faster transmission of both waves; so, reflected wave arrives earlier and causes a disproportionate increase in systolic pressure in the late systole (1). Augmentation of the central aortic pressure wave is expressed as augmentation pressure (AP) in absolute terms. Augmentation index (AIx) is the AP as a percentage of central pulse presure (2). Pulse waveform characteristics have been addressed as a determinant of cardiovascular morbidity and mortality (3,4). It was also reported that increased arterial wave reflections predicted severe cardiovascular events in patients undergoing percutaneous intervention (5).

In a study by Weber et al., noninvasively determined AIx and AP were associated with an increased risk of coronary artery disease (CAD) in younger and middle-aged male patients and when the extent of CAD was expressed as one-, two-, or three-vessel disease, there was a significant association between AP and the extent of CAD (6).

We aimed to investigate the association between noninvasively determined pulse waveform characteristics and the extent and severity of CAD objectively assessed using Gensini and SYNTAX scores, in patients undergoing coronary angiography with the clinical diagnosis of CAD.

Patients and methods

Patients older than 18 years who were decided to undergo coronary angiography with the clinical diagnosis of CAD between October 2012 and May 2013 were included. Exclusion criterions were prior percutaneous or surgical revascularization because

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Gensini and SYNTAX scores were validated in native CAD, more than mild valvular disease, severe renal or hepatic disease, and rhytm other than sinus. Patients whose heart rates were below 55 bpm and above 100 bpm prior to tonometric measurement were also excluded since AIx is affected by heart rate. Although during statistical analysis results would be adjusted for heart rate, we did not want to include extremes of heart rates.

Two hundred and eighteen patients were screened. Twenty-six of them were excluded because they had undergone prior revascularisation; eight patients had moderate valvular disease; 14 patients had atrial fibrillation; nine patients refused to sign the informed consent; five patients had more than moderate renal disease; 11 patients had heart rates below 55 bpm or above 100 bpm. Remaining 145 patients were included. Eighty-three had stable angina pectoris (SAP) which was defined as angina pectoris and/or angina equivalent symptoms suggestive of CAD and they had either positive stress test results or other indications for coronary angiography. Twenty-nine patients had unstable pattern of chest pain suggesting unstable angina pectoris (USAP) with or without ischemic electrocardiographic findings; and 33 patients were admitted with acute myocardial infarction (AMI). AMI was defined according to the latest universal definition of myocardial infarction (7).

Significant CAD was defined as the presence of at least 50% stenosis in at least one epicardial coronary artery. Minimal CAD was defined as CAD not fulfilling the criteria for significant CAD. Patients who were found to have normal coronary arteries (NCA) in coronary angiography constituted the NCA group. This study was conducted according to the recommendations of Declaration of Helsinki on Biomedical Research involving human subjects and was approved by the institutional ethics committee. Written informed consent was obtained from each participant.

Anthropometric parameters, medical history, presence of hypertension, diabetes and hyperlipidemia, smoking habits, family history of CAD and medications were recorded for each patient. Blood samples were drawn at admission for complete blood count, biochemistry, and lipid analysis.

Selective left and right coronary angiography was performed through femoral artery by standard Judkins technique with 6 Fr catheters (MediCath, Barcelona, Spain) using GE Innova 4100 (GE healthcare, Milwaukee, WI, USA). Extent and severity of CAD was assessed using Gensini and SYNTAX scores. Gensini score which considers both the extent and severity of the atherosclerotic lesions at coronary angiography was calculated for each patient (8). This scoring system grades the stenosis in the epicardial coronary arteries (1 for 1–25% stenosis, 2 for 26–50% stenosis, 4 for 51–75% stenosis, 8 for 76–90% stenosis, 16 for 91–99% stenosis, and 32 for total occlusion) and multiplies this number by a constant number determined according to the anatomical position of the lesion. Gensini score is zero when all epicardial coronary arteries are normal. Scores upto 20 are considered as minimal CAD, whereas scores more than 20 represent significant CAD (9). There is no upper limit for Gensini score; when there is extremely severe CAD, there may be values approaching 200 or more. SYNTAX score which is an anatomic scoring system developed to rank the complexity of CAD disease was calculated. Each lesion with more than 50% diameter stenosis in vessels more than 1.5 mm in diameter was scored using the online calculator version 2.1 at www.syntaxscore.com. A low SYNTAX score was defined as 22 or lesser, an intermediate score as 23–32, and a high score as 33 or greater (10). Patients with a SYNTAX score 23 or greater were considered to have moderate to severe CAD according to this definition.

Myocardial perfusion was assessed by myocardial blush grade (MBG) using the best projection for each coronary artery. Duration of cine filming was required to exceed three cardiac cycles in the washout phase to assess the washout of myocardial blush. Grade 0 was defined as the failure of the contrast to enter the microvasculature. In Grade 1, contrast slowly enters but fails to exit the microvasculature. Grade 2 defines delayed entry and exit from the microvasculature and Grade 3 means normal entry and exit from the microvasculature (11).

Noninvasive pulse waveform analysis (PWA) was performed on the day following coronary angiography with the commercially available SphygmoCor system (AtCor Medical, Sydney, Australia). Peripheral pressure waveforms were recorded from the radial artery, using applanation tonometry with a high-fidelity micromanometer. After the acquisition of 20 sequential waveforms, a validated (12) generalized transfer function was used to generate the corresponding central aortic pressure waveform. Only high-quality recordings, defined as an in device quality index 80% and visually acceptable curves by the investigator were included in the analysis. AP, AIx, and pulse pressure were recorded. The PWA examinations were performed in the sitting position under standardized conditions in the morning hours between 09.00 and 11.00 am and at least 2 hours after breakfast. The cardiologist who performed the analysis was experienced in this procedure and blinded to the coronary angiographic findings. Peripheral blood pressure measurements were performed with a validated automated arm blood pressure monitor keeping the radial artery at the level of

the heart. (Omron M3W, Omron Healthcare). Blood pressure recordings were immediately made prior to tonometric measurements. The average of two measurements taken at 5-minute intervals was recorded.

Statistical analyses

The SPSS statistical software (SPSS 15.0 for windows, Inc., Chicago, IL, USA) was used for all statistical calculations. Kolmogorov–Smirnov test was used to test for normal distribution. Continuous variables were given as mean ± standard deviation and medians (range); categorical variables were defined as percentages. Continuous variables were compared by t-test and ANOVA for normally distributed variables. Mann–Whitney U and Kruskal–Wallis tests were used for nonnormally distributed variables. For post hoc multiple comparisons Bonferroni's correction was made. χ^2 test was used for the categorical variables between two groups. Spearman's correlation coefficient was used for the analysis of the correlation between AP, Aix, and Gensini and SYNTAX scores. Partial correlation coefficients were calculated taking age, gender, height, heart rate, hypertension, and diabetes into consideration. An optimal cut-off value to predict the presence of significant CAD and the presence of moderate to severe CAD by AIx was determined using receiver operating characteristics (ROC) analysis and area under curve (AUC) values were determined. Logistic regression analysis with Backward LR method was used for multivariate analysis of independent variables, which were significantly different in univariate analysis. After exclusion of irrelevant variables ($p > 0.05$) from the model, logistic regression analysis with enter method was performed with remaining significant variables and then Odds ratio (OR) for having moderately severe CAD expressed as SYNTAX 23 or greater was presented. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$.

Results

Baseline characteristics of the study population are demonstrated in Table I. There were no significant differences with respect to age, presence of risk factors, and use of medications between female and male patients. However, the percentage of male patients with significant CAD was higher than females. In contrary, more females had NCA. Males had higher uric acid and lower HDL levels than females. Coronary angiographic findings are also represented in Table I. Males had more extensive and severe CAD expressed as higher Gensini and SYNTAX scores. In the entire study population without sex discrimination, 72 patients had significant CAD with a median Gensini score of 40.5 (5–210) and SYNTAX score of 25.5 (5–47); 33 patients had minimal CAD with a median Gensini score of 6.5 (2–15) and 40 patients had NCA.

Table I. Baseline characteristics of the study population with respect to gender.

	Female (N:67)	Male (N:78)	p
Age (years)	60.5 ± 11.7	59.7 ± 14.7	0.744
HT (%)	56.7	56.4	0.552
DM (%)	29.9	37.2	0.226
HPL (%)	52.2	64.1	0.101
FH (%)	31.3	30.8	0.541
Smoker (%)	46.2	53.8	0.146
Anti-DM (%)	28.4	30.8	0.447
Anti-HT (%)	55.2	61.5	0.274
ACEI	29.9	37.2	0.383
BB	29.8	26.9	0.715
CCB	32.8	25.6	0.364
Statin (%)	28.4	42.3	0.057
Significant CAD (%)	35.8	61.5	0.002
Minimal CAD (%)	19.4	25.6	0.244
NCA (%)	44.8	12.8	< 0.001
Hb (g/dL)	128 ± 14	143 ± 19	< 0.001
WBC (10^9/L)	8.1 ± 3.6	7.6 ± 2.1	0.319
Plt (10^9/L)	276.4 ± 94.5	232.8 ± 57.5	0.001
BUN (mmol/L)	5.82 ± 2.93	6.1 ± 2.43	0.545
Creatinin (μmol/L)	69.8 ± 44.2	80.4 ± 26.5	0.104
u.acid (μmol/L)	292.7 ± 83.3	345.1 ± 84.49	< 0.001
LDL (mmol/L)	3.16 ± 0.9	131.6 ± 36.1	0.103
HDL (mmol/L)	1.25 ± 0.45	1.06 ± 0.3	0.004
TG (mmol/L)	1.62 ± 0.59	1.88 ± 1.479	0.158
EF (%)	58.9 ± 7.3	56.6 ± 8.6	0.08
Gensini	4.5 (0–136)	16.3 (0–210)	0.01
SYNTAX	0 (0–44)	14 (0–47)	0.002
MBG	3 (0–3)	3 (0–3)	0.950

ACE-I, angiotensin converting enzyme inhibitör; Anti-DM, antidiabetic medication; anti-HT, antihypertensive medication; BB, beta blocker; BUN, blood urea nitrogen; CAD, coronary artery disease; CCB, calcium channel clocker; DM, diabetes mellitus; EF, ejection fraction; FH, family history; Hb, hemoglobin; HDL, high density lipoprotein; HPL, hyperlipidemia; HT, hypertension; LDL, low density lipoprotein; MBG, myocardial blush grade; NCA, normal coronary arteries; plt, platelet; TG, triglyceride; WBC, white blood cell count; u.acid, uric acid.

Table II shows the hemodynamic and central PWA data separately for females and males in significant CAD, minimal CAD, and NCA groups. In both sexes, AP and AIx were significantly higher in significant CAD patients. Table III shows the hemodynamic and central PWA data with respect to mild, moderate, and high SYNTAX scores again demonstrated seperately for male and female patients.

When patients were divided into two subgroups with respect to the presence of diabetes mellitus, mean AP of diabetics was 10.0 ± 2.2 and non-diabetics was 8.8 ± 2.3 (p: 0.004), whereas mean AIx of diabetics

Table II. Hemodynamic and pulse wave analysis data with respect to the presence of significant CAD, minimal CAD, and normal coronary arteries.

	Significant CAD (F:24, M:48)	Minimal CAD (F:13, M:20)	NCA (F:30, M:10)	p
Brachial SBP (mmHg)	F 138.8 ± 13	133.3 ± 10.5	137.9 ± 10.7	0.366
	M 139.6 ± 12.7	138.3 ± 13.2	130.9 ± 11.1	0.145
Brachial DBP (mmHg)	F 86.3 ± 9.2	81.6 ± 8.4	86.3 ± 8.9	0.246
	M 86.3 ± 9.3	84.4 ± 10.0	79.4 ± 8.0	0.105
Central SBP (mmHg)	F 127 ± 12.7	121.4 ± 10.9	126.2 ± 10.7	0.341
	M 127.9 ± 12.8	127.0 ± 13.6	118.7 ± 10.8	0.124
Central DBP (mmHg)	F 86.4 ± 9.2	81.8 ± 8.5	86.3 ± 8.7	0.260
	M 86.7 ± 9.5	84.6 ± 10.1	80.2 ± 8.2	0.140
Central PP (mmHg)	F 40.6 ± 6.3	39.5 ± 5.1	39.9 ± 5.4	0.842
	M 41.2 ± 5.9	42.4 ± 6.8	38.5 ± 4.9	0.262
HR (beats/min)	F 72 ± 7.1	69.7 ± 5.6	69.6 ± 7.4	0.426
	M 70.8 ± 6.9	72.1 ± 6.0	67.3 ± 5.8	0.171
AP (mmHg)	F 10.1 ± 2.5	8.2 ± 1.7	7.8 ± 2.0	0.001[a]
	M 10.2 ± 1.9	9.2 ± 2.3	7.2 ± 1.8	< 0.001[b]
AIx (mmHg)	F 24.8 ± 3.3	20.6 ± 2.7	19.5 ± 2.9	< 0.001[c]
	M 24.9 ± 2.9	21.6 ± 3.0	18.6 ± 2.6	< 0.001[d]

AIx, augmentation index; AP, augmentation pressure; CAD, coronary artery disease; DBP, diastolic blood pressure; NCA, normal coronary arteries; SBP, systolic blood pressure; PP, pulse pressure.
[a]p value for NCA—significant CAD: 0.001, minimal CAD—significant CAD: 0.027.
[b]p value for NCA—minimal CAD: 0.036, NCA—significant CAD: < 0.001.
[c]p value for NCA—significant CAD: < 0.001, minimal CAD—significant CAD: < 0.001.
[d]p value for NCA—minimal CAD: 0.027, NCA—significant CAD: < 0.001 and minimal CAD—significant CAD: < 0.001.

Table III. Hemodynamic data in different severities of CAD according to SYNTAX score with respect to gender.

	NCA (F:30, M:10)	SYNTAX ≤ 22 (F:23, M:38)	SYNTAX 23–33 (F:9, M:16)	SYNTAX ≥ 33 (F:5, M:14)	p
Brachial SBP (mmHg)	F 137.9 ± 10.7	135.0 ± 9.1	140.8 ± 17.7	138.6 ± 14.8	0.600
	M 130.9 ± 11.1	138.3 ± 11.9	141.1 ± 14.5	139.7 ± 13.7	0.147
Brachial DBP (mmHg)	F 86.3 ± 8.9	83.3 ± 7.7	85.9 ± 10.9	88.4 ± 11.9	0.554
	M 79.4 ± 8.0	85.3 ± 9.3	86.5 ± 10.1	86.0 ± 9.6	0.204
Central SBP (mmHg)	F 126.2 ± 10.7	122.9 ± 9.4	129.2 ± 17.5	127 ± 13.5	0.529
	M 118.7 ± 10.8	127.0 ± 12.0	129.3 ± 15.2	127.4 ± 13.4	0.107
Central DBP (mmHg)	F 86.3 ± 8.7	83.6 ± 7.8	85.9 ± 10.9	88.4 ± 11.9	0.612
	M 80.2 ± 8.2	85.5 ± 9.4	86.9 ± 10.4	86.6 ± 9.9	0.253
Central PP (mmHg)	F 39.9 ± 5.4	39.3 ± 4.9	43.3 ± 7.7	38.6 ± 5.4	0.291
	M 38.5 ± 4.9	41.4 ± 6.4	42.4 ± 6.8	40.8 ± 4.8	0.181
Heart rate (beats/min)	F 69.6 ± 7.4	71.0 ± 6.0	71.4 ± 7.8	71.6 ± 8.8	0.840
	M 67.3 ± 5.8	71.5 ± 6.5	71.2 ± 5.6	70.1 ± 8.2	0.181
AP (mmHg)	F 7.8 ± 2.0	8.3 ± 1.4	12.0 ± 2.8	10.2 ± 1.6	< 0.001[a]
	M 7.2 ± 1.8	9.1 ± 1.9	11.0 ± 2.2	11.0 ± 1.3	< 0.001[b]
AIx (mmHg)	F 19.5 ± 2.9	21.0 ± 2.4	27.4 ± 2.2	26.5 ± 1.3	< 0.001[c]
	M 18.6 ± 2.6	21.9 ± 2.6	26.0 ± 2.5	27.1 ± 0.9	< 0.001[d]

AIx, augmentation index; AP, augmentation pressure; DBP, diastolic blood pressure; NCA, normal coronary arteries; SBP, systolic blood pressure; PP, pulse pressure.
[a]p value for NCA – SYNTAX 23–33: < 0.001, NCA – SYNTAX ≥ 33: 0.011, SYNTAX ≤ 22 – SYNTAX 23–33: < 0.001, SYNTAX ≤ 22 – SYNTAX ≥ 33: 0.041.
[b]p value for NCA – SYNTAX ≤ 22: 0.007, NCA – SYNTAX 23–33: < 0.001, NCA – SYNTAX ≥ 33: < 0.001, SYNTAX ≤ 22 – SYNTAX 23–33: 0.001, SYNTAX ≤ 22– SYNTAX ≥ 33: 0.001.
[c]p NCA – SYNTAX ≤ 22: 0.031, NCA – SYNTAX 23–33: < 0.001, NCA – SYNTAX ≥ 33: < 0.001, SYNTAX ≤ 22 – SYNTAX 23–33: < 0.001, SYNTAX ≤ 22 – SYNTAX ≥ 33: < 0.001.
[d]p value for NCA – SYNTAX ≤ 22: < 0.001, NCA – SYNTAX 23–33: < 0.001, NCA – SYNTAX ≥ 33: < 0.001, SYNTAX ≤ 22 – SYNTAX 23–33: < 0.001, SYNTAX ≤ 22 – SYNTAX ≥ 33: < 0.001.

was 24.4 ± 2.8 and nondiabetics was 21.5 ± 3.9 ($p < 0.001$).

Dividing the patients according to tertiles of AIx, the percentage of patients who were admitted with AMI was higher in the third tertile ($p < 0.001$). In addition, significantly higher percentage of patients in the third tertile was found to have significant CAD evidenced by higher Gensini and SYNTAX scores and lower MBG (Table IV).

The AIx value to predict the presence of significant CAD was 22.55% (ROC analysis AUC: 0.86; sensitivity: 75%, specificity: 75%, 95% CI: 0.80–0.92, $p < 0.001$) (Figure 1); whereas the AIx value to predict the presence of moderate to severe CAD as determined by SYNTAX score 23 or more was 24.45% (ROC analysis AUC: 0.96; sensitivity: 88%, specificity: 93%, 95% CI: 0.93–0.99, $p < 0.001$) (Figure 2).

Table V demonstrates the results of the univariate and multivariate logistic regression analysis for having moderately severe CAD expressed as SYNTAX score 23 or more. OR of AIx was detected as 2.95 (95% CI: 1.93–4.50, $p < 0.001$). In addition, AIx was significantly correlated with Gensini and SYNTAX scores in all three clinical presentations after adjustment for age, gender, height, presence of hypertension, heart rate, and diabetes (Table VI).

Discussion

We have demonstrated that increased AIx assessed noninvasively using central PWA was associated with the presence of significant CAD. In addition, it was correlated with Gensini and SYNTAX scores both in stable patients and in patients with acute coronary syndromes; and we provided a cut-off value to predict the presence of significant CAD and moderate to severe CAD according to SYNTAX score.

There are studies reporting an association between central aortic wave reflection and CAD; but the correlation between extent and severity of coronary atherosclerosis and central PWA is a matter of controversy. Lekakis et al. found that AIx was a marker of extensive extracoronary atherosclerosis but no relationship existed between Gensini score or number of diseased vessels and AIx (13). Gaszner

Table IV. Coronary artery disease risk factors, coronary angiographic findings and presentation clinics with respect to tertiles of augmentation index.

	AIx tertile 1 (N:48)	AIx tertile 2 (N:50)	AIx tertile 3 (N:47)	p
Age (years)	51.1 ± 11.7	62.8 ± 11.1	66.3 ± 12.6	< 0.001[a]
Presentation				
SAP (%)	73	70	28	< 0.001[b]
USAP (%)	25	20	15	0.469
AMI (%)	2	10	57	< 0.001[c]
DM (%)	8.3	46	46.8	< 0.001[d]
HT (%)	33.3	68	68.1	< 0.001[e]
Smoker (%)	60.4	42	53.2	0.184
FH (%)	41.7	30	21.3	0.098
HPL (%)	43.8	66	65.9	0.038[f]
Significant CAD (%)	6.9	36.1	56.9	< 0.001[g]
SYNTAX score	0 (0–12)	7 (0–27)	30 (0–47)	< 0.001[h]
Gensini score	0 (0–26)	12.8 (0–42.5)	48 (0–210)	< 0.001[i]
MBG	3 (2–3)	3 (1–3)	2 (0–3)	< 0.001[j]

AIx, augmentation index; AMI, acute myocardial infarction; CAD, coronary artery disease; MBG, TIMI myocardial blush grade; USAP, unstable angina pectoris; SAP, Stable angina pectoris. $p < 0.05$ is considered significant for means and percentages. For medians, $p < 0.017$ is considered significant after Bonferroni's correction.

[a]p value for AIx tertile 1-AIx tertile 2: < 0.001; AIx tertile 1-AIx tertile 3: < 0.001.

[b]p value for AIx tertile 1-AIx tertile 3: $p < 0.001$; AIx tertile 2-AIx tertile 3: $p < 0.001$.

[c]p value for AIx tertile 1-AIx tertile 3: < 0.001; AIx tertile 2-AIx tertile 3: $p < 0.001$.

[d]p value for AIx tertile 1-AIx tertile 2: < 0.001; AIx tertile 1-AIx tertile 3: < 0.001.

[e]p value for AIx tertile 1-AIx tertile 2: 0.001; AIx tertile 1-AIx tertile 3: 0.001.

[f]p value for AIx tertile 1-AIx tertile 2: 0.042; AIx tertile 1-AIx tertile 3: 0.04.

[g]p value for AIx tertile 1-AIx tertile 2: < 0.001; AIx tertile 1-AIx tertile 3: < 0.001 AIx tertile 2-AIx tertile 3: $p < 0.001$.

[h]p value for AIx tertile 1-AIx tertile 2: < 0.001; AIx tertile 1-AIx tertile 3: < 0.001 AIx tertile 2-AIx tertile 3: $p < 0.001$.

[i]p value for AIx tertile 1-AIx tertile 2: < 0.001; AIx tertile 1-AIx tertile 3: < 0.001 AIx tertile 2-AIx tertile 3: $p < 0.001$.

[j]p value for AIx tertile 1-AIx tertile 3: < 0.001; AIx tertile 2-AIx tertile 3: $p < 0.001$.

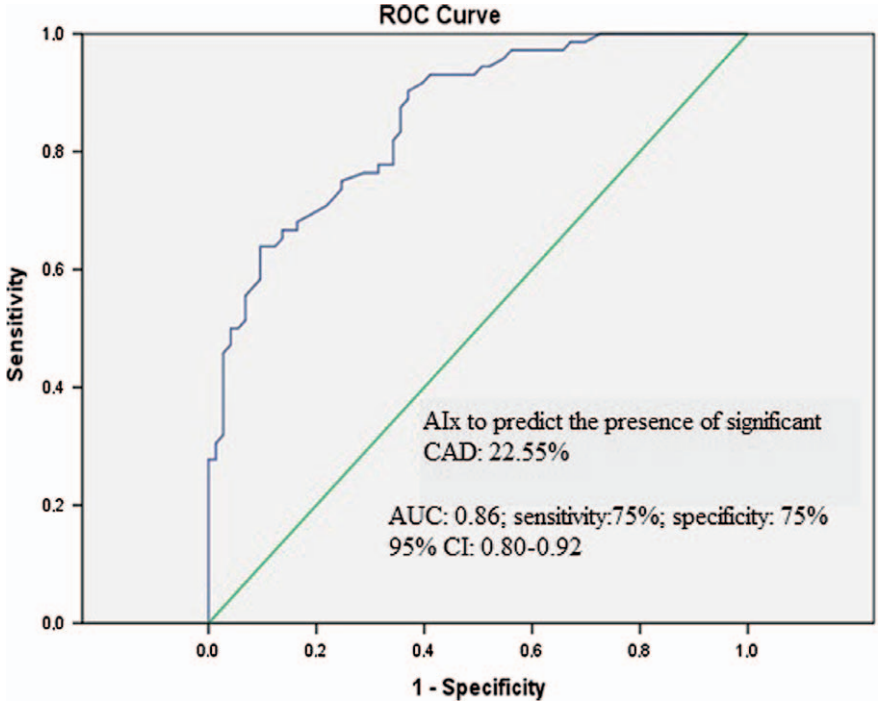

Figure 1. ROC curve demonstrating the augmentation index (AIx) cut-off value to predict the presence of significant CAD.

et al. reported that AIx values measured with an oscillometric occlusive device were higher in patients with verified CAD than those in the control patients. However, they did not find a significant correlation between the AIx and SYNTAX scores (14).

In contrary, Weber et al. found that, in patients up to the age of 60, noninvasively determined AP and AIx were related to the presence and to the extent of CAD expressed as one-, two-, or three-vessel disease (6). In a very recent study, Cho et al. have shown that AIx and pulse pressure amplification were associated with an increased risk of three-vessel disease in patients younger than 65 years. In addition, they were also correlated with the severity of CAD using

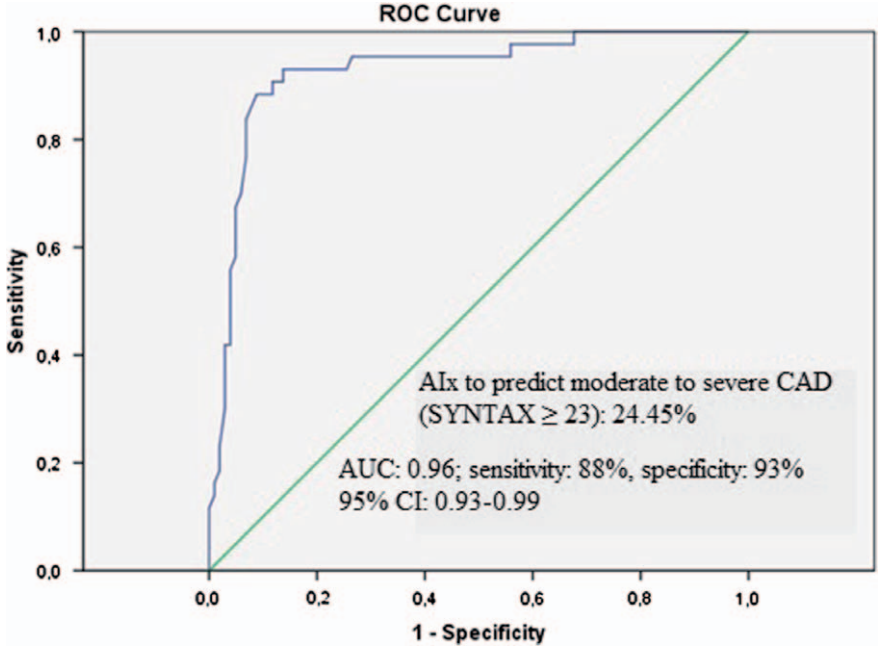

Figure 2. ROC curve demonstrating the augmentation index (AIx) cut-off value to predict moderate to severe CAD according to SYNTAX score.

Table V. Univariate and multivariate analysis using the logistic regression method for the presence of moderately severe coronary artery disease (SYNTAX ≥ 23).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age (years)	1.06	(1.03–1.09)	< 0.001	0.98	(0.60–8.50)	0.227
Sex (male)	2.24	(1.06–4.73)	0.034	1.59	(0.39–6.42)	0.516
ACS (vs SAP)	6.98	(3.12–15.64)	< 0.001	2.26	(0.60–8.50)	0.227
AIx	2.94	(2.03–4.25)	< 0.001	2.95	(1.93–4.50)	< 0.001
SBP	1.03	(1.0–1.06)	0.062			
DM	2.91	(1.39–6.11)	0.005	1.36	(0.37–5.02)	0.646

ACS, acute coronary syndrome (unstable angina pectoris + acute myocardial infarction); AIx, augmentation index; CI, confidence interval; DM, diabetes mellitus; OR, Odds Ratio; SAP, stable angina pectoris; SBP, systolic blood pressure.

Gensini score (15). The conflicting results of different studies may be due to variations in the sample sizes, different methods, and devices used for the measurement of AIx and different study designs most of which are cross-sectional and non-randomized.

The present study is in good accordance with those which relate increased aortic wave reflections with CAD; but, to the best of our knowledge, it is the first to report a significant association between AIx and SYNTAX scores. SYNTAX score has gained popularity in the last decade for assessment of native CAD taking lesion characteristics into account. SYNTAX score is important because it has prognostic implications in terms of death, cardiac death, myocardial infarction, and target vessel revascularization in patients with acute coronary syndromes (16). So it is a much more precise expression rather than crudely classifying CAD as the number of diseased vessels.

We demonstrated that AP and AIx were higher in patients with more severe and complex CAD, and this association was equally evident in both sexes. We have shown a significant positive correlation between AIx, Gensini and SYNTAX scores seperately in SAP, USAP, and AMI adjusting for age, gender, heart rate, height, hypertension, and diabetes. Although the exact mechanism underlying the relationship between central pulse wave amplification and the severity of CAD cannot be clarified because of the cross-sectional nature of the study, there are possible suggestions. A possible explanation could be reduced coronary perfusion due to increased afterload caused by increased pulse pressure amplification (17,18). Kingwell et al. have shown that arterial stiffness and compliance indices including carotid AIx were associated with myocardial ischemic threshold as assessed by time to ST-segment threshold during a treadmill exercise test (19). It is proposed that increased aortic pulse pressure might cause vascular endothelial damage which is the promoter to initiate atherosclerotic lesions (20). Thacher et al. have shown that altered pulsatile hemodynamics and increased shear stress cause endothelial dysfunction via decreased nitric oxide (NO) bioavailability (21). Furthermore, AIx was found to be significantly associated with plasma levels of asymmetric dimethylarginine which is an endogenous inhibitor of endothelial NO synthase (22).

Table VI. Correlation coefficients for the association between augmentation index, Gensini and SYNTAX scores adjusted for age, gender, height, heart rate, presence of hypertension or diabetes in three different clinical presentations.

Presentation	Association	r	p
SAP	AIx-Gensini	0.352	0.002
	AIx-SYNTAX	0.456	< 0.001
USAP	AIx-Gensini	0.651	0.001
	AIx-SYNTAX	0.564	0.006
AMI	AIx-Gensini	0.459	0.018
	AIx-SYNTAX	0.564	0.003

AMI, acute myocardial infarction; AIx, augmentation index; USAP, unstable angina pectoris; SAP, stable angina pectoris. $P < 0.05$ is considered significant.

In a recent study reporting 6.5 years follow-up results of 1300 men and 1773 women, noninvasively measured AIx was found to be associated with all-cause mortality and combined cardiovascular end point including time to first myocardial infarction, ischemic cerebrovascular disease, percutaneous coronary intervention, and coronary artery by-pass graft in men but not in women (23). Prognostic implications of the association between AIx and CAD if any, remains to be elucidated by prospective randomized studies which would also shed light on mechanistic considerations.

The main limitation of the study was the relatively small sample size recruited in a single center. In addition, we did not stratify our study population with respect to age in addition to gender because of sample size considerations. In previous studies, it was noted that age-dependent alterations in AIx was more prominent up to the age of 60 after which there

was a plateu (16). This was due to dominance of reflected wave before 60 years of age, whereas equal contribution of the incident and reflected waves after that (24). In the present study, the mean age of both sexes were very close to 60. More importantly, we have adjusted the results for age in addition to other possible confounders.

In the present study we included patients with a wide spectrum of clinical presentations which made the study population inhomogeneous. However, it is noteworthy to have detected that significant correlations exist between AIx and severity of CAD in all three presentations.

In conclusion, increased AIx assessed noninvasively using PWA is associated with the presence, severity, and complexity of CAD objectively assessed by SYNTAX score. The exact mechanism remains to be elucidated by prospective studies; but it may be used in selected patients during cardiovascular evaluation in outpatient settings for risk stratification purposes prior to coronary angiography.

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