

Arterial Stiffness, Wave Reflections, and the Risk of Coronary Artery Disease

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Background—Increased arterial stiffness, determined invasively, has been shown to predict a higher risk of coronary atherosclerosis. However, invasive techniques are of limited value for screening and risk stratification in larger patient groups.

Methods and Results—We prospectively enrolled 465 consecutive, symptomatic men undergoing coronary angiography for the assessment of suspected coronary artery disease. Arterial stiffness and wave reflections were quantified noninvasively using applanation tonometry of the radial artery with a validated transfer function to generate the corresponding ascending aortic pressure waveform. Augmented pressure (AP) was defined as the difference between the second and the first systolic peak, and augmentation index (AIx) was AP expressed as a percentage of the pulse pressure. In univariate analysis, a higher AIx was associated with an increased risk for coronary artery disease (OR, 4.06 for the difference between the first and the fourth quartile [1.72 to 9.57; $P < 0.01$]). In multivariate analysis, after controlling for age, height, presence of hypertension, HDL cholesterol, and medications, the association with coronary artery disease risk remained significant (OR, 6.91; $P < 0.05$). The results were exclusively driven by an increase in risk with premature vessel stiffening in the younger patient group (up to 60 years of age), with an unadjusted OR between AIx quartiles I and IV of 8.25 ($P < 0.01$) and a multiple-adjusted OR between these quartiles of 16.81 ($P < 0.05$).

Conclusions—AIx and AP, noninvasively determined manifestations of arterial stiffening and increased wave reflections, are strong, independent risk markers for premature coronary artery disease. (*Circulation*. 2004;109:184-189.)

Key Words: coronary disease ■ waves ■ arteries ■ arteriosclerosis

Pulse pressure, reflecting the pulsatile component of blood pressure and thus to some extent arterial stiffness,¹ is a well-known risk factor for myocardial infarction,^{2,3} particularly in men.⁴ More accurate determinations of the elastic properties of the aorta and the large arteries, including angiographic measures,⁵ echocardiography,⁶ ultrasound measures of abdominal aortic and carotid arterial diameter,⁷ MRI,⁸ radionuclide angiography,⁹ and pulse wave velocity,^{10,11} have shown associations with coronary atherosclerosis. The central aortic pressure wave is composed of a forward-traveling wave generated by left ventricular ejection and a later-arriving reflected wave from the periphery.¹² As aortic and arterial stiffness increase, transmission velocity of both forward and reflected waves increase, which causes the reflected wave to arrive earlier in the central aorta and augment pressure in late systole. Therefore, augmentation of the central aortic pressure wave is a manifestation of early wave reflection and is the boost of pressure from the first systolic shoulder to the systolic pressure peak.¹³ This can be expressed in absolute terms (augmented pressure [AP]) or as a percentage of pulse pressure (augmentation index [AIx]).

AIx, determined invasively, has been shown to be predictive for coronary artery disease (CAD).¹⁴ Because a noninvasive approach clearly would be of value for the examination of larger populations, we investigated the association between CAD and aortic AIx, assessed by noninvasive pulse wave-form analysis (PWA).

Methods

This study was conducted in an invasive cardiology department in a 1050-bed tertiary referral hospital in Austria. We included 465 consecutive, unselected male patients undergoing coronary angiography for the diagnosis or exclusion of CAD. Patients with more than mild valvular heart disease were excluded. All patients were studied while taking regular medications (drugs were not withheld before measurement) and gave written informed consent. The study was approved by our local ethics committee.

Hypertension was present with repeated measurements of ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic blood pressure or permanent antihypertensive drug treatment. Diabetes mellitus was defined as a fasting blood glucose concentration ≥ 126 mg/dL or antihyperglycemic drug treatment. Current smoking was defined as having smoked the last cigarette less than 1 week before coronary angiography.

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Coronary Angiography

All patients underwent routine coronary angiography using the Judkins technique on digitized coronary angiography equipment (Cathcor, Siemens). All coronary angiograms were visually assessed by at least 3 experienced angiographers (case load >5000 angiograms each), and a consensus was reached. The reviewers were blinded to the results of PWA. For this study, we defined significant CAD as at least 1 50% or greater diameter stenosis in at least 1 coronary vessel or prior percutaneous or surgical coronary revascularization. The extent of CAD was defined as (1) 1-, 2-, or 3-vessel disease and (2) addition of a modified stenosis score system (minimum score was 0; maximum score was 27),¹⁵ with 0, 1, 2, and 3 points, respectively, for <50%, 50% to 70%, 71% to 89%, and \geq 90% diameter stenosis in 1 to 3 segments of the 3 main coronary arteries (a total of 9 segments). The absence of CAD was defined as completely smooth epicardial coronary arteries without any narrowings visible on coronary angiogram.

Pulse Waveform Analysis

Assessment of arterial stiffness was performed noninvasively with the commercially available SphygmoCor system (AtCor Medical). In brief, peripheral pressure waveforms were recorded from the radial artery at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments). After 20 sequential waveforms had been acquired, a validated^{16–18} generalized transfer function was used to generate the corresponding central aortic pressure waveform. AIx and AP were derived from this with the technique of PWA.¹⁹ The merging point of the incident and the reflected wave (the inflection point) was identified on the generated aortic pressure waveform. AP was the maximum systolic pressure minus pressure at the inflection point. The AIx was defined as the AP divided by pulse pressure and expressed as a percentage. Larger values of AIx indicate increased wave reflection from the periphery or earlier return of the reflected wave as a result of increased pulse wave velocity (attributable to increased arterial stiffness) and vice versa. In addition, because AIx is influenced by heart rate, an index normalized for heart rate of 75 bpm (AIx@75) was used in accordance with Wilkinson et al.²⁰ Time to return of the reflected wave (Tr) was the time from the beginning of the derived aortic systolic pressure waveform to the inflection point and can be used as a substitute for pulse wave velocity (a higher pulse wave velocity will lead to a shorter Tr).²¹ Only high-quality recordings, defined as an in-device quality index \geq 80% (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) and acceptable curves on visual inspection by 1 investigator (T.W.), were included in the analysis. A total of 19% of the patients initially evaluated had inadequate pressure tracings, leaving 465 patients for the study. These exclusions occurred mainly at the beginning of the study (75% of the tracings were acceptable during the first 2 months of the study and 93% during the final months). All PWA measurements were taken in the sitting position in a quiet, temperature-controlled room ($22 \pm 1^\circ\text{C}$) after a brief period (at least 5 minutes) of rest, most often on the day after cardiac catheterization by nurses not involved in performance or interpretation of the angiograms. Repeatability of PWA was good. According to the Bland-Altman method, mean differences between consecutive AIx and AP measurements performed on 2 different days were 1.37% and 1.2 mm Hg, respectively; 95% limits of agreement for AIx and AP were 10.1% and 9.6 mm Hg, respectively (Figure 1).

Blood pressure measurements were performed with a validated,²² automated wrist blood pressure monitor (Omron R3, Omron Healthcare), with the radial artery kept at heart level during measurement.

Statistics

Values are expressed as mean \pm 1 SD. Categorical variables were compared using the χ^2 test. Differences in the mean values between the 2 groups were compared using unpaired *t* test, and numerical correlations were established by a Spearman correlation. A *P* value of <0.05 was considered significant. Crude rates were compared by

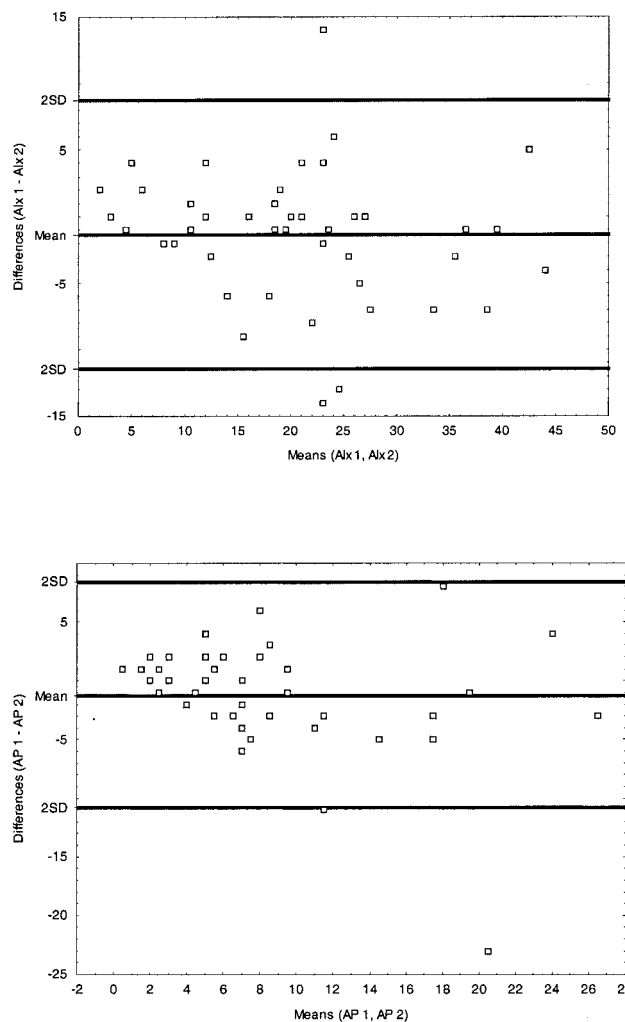


Figure 1. A and B, Bland-Altman plots of 2 AIx and AP measurements on 2 different days. Mean values vs differences.

Pearson-Mantel-Haenszel test, except the continuous per quartile result, which was calculated using the logistic regression model. Statistical analyses were performed using Statistica 6.0 (StatSoft Inc) as well as BiAS for Windows, 7.05 (Hanns Ackermann) software packages.

Results

Baseline Clinical Characteristics

The baseline clinical characteristics of our patients are summarized in Table 1. Patients with CAD were older, had more traditional risk factors, had a higher pulse pressure, and used β -blockers, ACE inhibitors, and nitrates more frequently. Of note, the difference in pulse pressure was mediated mainly by a lower diastolic blood pressure in the CAD group, not by higher systolic pressure. This is consistent with a greater degree of arterial stiffness and lower coronary perfusion pressure in this group.

AP, AIx, AIx@75, Tr, and CAD: Univariate Analysis

In the entire study population, indices of arterial stiffness and wave reflections were associated significantly with CAD (Table 2). When patients were classified into quar-

TABLE 1. Baseline Characteristics of Study Patients

	CAD	No CAD	Level of Significance, <i>P</i> Value
No. of patients	406	59	
Body height, cm	171.2±6.6	174.9±6.9	0.00008
Age, y	63.8±10.3	53.7±11.7	<0.000001
Hypertension (%)	285 (70)	28 (47)	0.005
Current smokers (%)	87 (21)	14 (24)	0.84
Diabetes (%)	88 (22)	6 (10)	0.15
Total cholesterol, mg/dL	199.7±44.9	203.1±37.4	0.58
LDL cholesterol, mg/dL	121.3±40.7	117.5±33.1	0.56
HDL cholesterol, mg/dL	42.6±11.5	46.0±13.1	0.06
Triglycerides, mg/dL	179.2±125.4	190.8±131.6	0.51
Creatinine, mg/dL	1.25±0.73	1.12±0.19	0.15
Heart rate, bpm	65.4±12.2	67.5±12.7	0.22
Peripheral systolic blood pressure, mm Hg	131.9±19.9	130.9±17.8	0.73
Peripheral diastolic blood pressure, mm Hg	78.3±13.7	83.2±11.2	0.009
Peripheral pulse pressure, mm Hg	53.6±15.5	47.7±15.0	0.007
Calculated aortic systolic blood pressure, mm Hg	118.8±18.9	118.7±17.1	0.96
Calculated aortic diastolic blood pressure, mm Hg	78.9±13.8	84.3±10.9	0.005
Calculated aortic pulse pressure, mm Hg	39.9±13.0	34.4±13.3	0.003
Normal left ventricular function (%)	322 (79)	49 (83)	0.87
Ejection fraction, %	58.8±12.4	60.4±17.3	0.53
Angio-score	6.3±3.8	0±0	<0.0000001
Medications (%)			
Nitrates	168 (41)	6 (10)	0.0001
β-blockers	244 (60)	19 (32)	0.0005
ACE inhibitors	180 (44)	14 (24)	0.01
Angiotensin receptor blockers	14 (3)	1 (2)	0.83
Calcium channel blockers	49 (12)	3 (5)	0.39
α-Adrenergic blockers	1 (<1)	0 (0)	0.97
Diuretics	102 (25)	9 (15)	0.22
Statins	204 (50)	7 (12)	0.000002

Values are mean±SD or No. (%).

tiles of AIx, the OR for the presence of CAD for patients with highest versus lowest AIx was 4.06 ($P<0.01$) (Table 3).

After dividing patients into a younger (up to 60 years of age, 190 patients) and an older (older than 60 years of age, 275 patients) group, we found that AP, AIx, AIx@75, and Tr were different in patients with or without CAD in the younger age group only (Table 2). However, these differences were more pronounced than in the total group. Using the same quartiles of AIx again (Figure 2), the OR for the presence of CAD for patients with highest versus lowest AIx was 8.25 ($P<0.01$).

Because AIx is dependent on heart rate, we also corrected for this (as stated above). The differences between CAD and non-CAD patients were apparent with the derived AIx@75 as well (Table 2).

Pulse Waveform Analysis and the Severity of CAD

In the whole patient group, there were weak albeit statistically significant correlations between AP and AIx@75, but not AIx and Tr, and the extent of CAD, expressed as angio-score. This was age-dependent; in the older group (>60 years), AIx, AP, and AIx@75 were high in virtually all patients and were not related to the extent of coronary atherosclerosis. However, in the younger patient group, these correlations were stronger and present for AP, AIx, AIx@75, and Tr, thus being markers of premature stiffness and coronary atherosclerosis as well (Table 5). When the severity of CAD was expressed as 1-, 2-, or 3-vessel disease or no CAD (after excluding patients with prior percutaneous revascularization but no recent coronary stenosis) in this younger patient group, again there was a

TABLE 2. AIx, AP, AIx75, and Tr and the Risk for CAD in All Patients and in the Younger (≤ 60 Years of Age) and Older (> 60 Years of Age) Patients Groups

	CAD	No CAD	Level of Significance, P Value
Total patient group, n=465	406	59	...
Age, y	63.8 \pm 10.3	53.7 \pm 11.7	<0.000001
AIx	21.5 \pm 11.7	17.1 \pm 12.0	0.007
AP, mm Hg	9.1 \pm 6.3	6.6 \pm 6.6	0.004
AIx@75	16.9 \pm 9.9	13.4 \pm 10.6	0.01
Tr, msec	138.5 \pm 12.3	142.2 \pm 15.1	0.04
Younger patient group, n=190	146	44	...
age, y	52.4 \pm 5.5	48.5 \pm 8.2	0.0004
AIx	22.4 \pm 11.6	15.4 \pm 11.6	0.0005
AP, mm Hg	8.6 \pm 5.5	5.1 \pm 5.0	0.0002
AIx@75	17.2 \pm 9.4	11.7 \pm 10.3	0.002
Tr, msec	139.9 \pm 11.9	144.3 \pm 16.3	0.05
Older patient group, n=275	260	15	...
Age, y	70.2 \pm 5.8	69.1 \pm 5.3	0.45
AIx	21.0 \pm 11.7	22.1 \pm 12.3	0.74
AP, mm Hg	9.4 \pm 6.7	10.9 \pm 8.9	0.43
AIx@75	16.7 \pm 10.2	18.1 \pm 10.1	0.61
Tr, msec	137.7 \pm 12.5	135.9 \pm 8.6	0.57

significant association between the extent of CAD and AP (Figure 3).

Multivariate Analysis

After adjustment for age, height, hypertension, HDL cholesterol, and the use of β blockers, ACE inhibitors, statins, and nitrates, the association between AIx and CAD risk remained significant (OR for the presence of CAD for patients with highest versus lowest AIx 6.91, $P < 0.05$) (Table 3). Again, this association was greater in the younger patient group (OR 16.81, $P < 0.05$) (Table 4).

Discussion

In the present study, we observed for the first time a strong and independent association between manifestations of increased arterial stiffness and early wave reflections, derived from noninvasive PWA, and the presence and, to some extent, severity of CAD. Increased AIx and arterial stiffness

are associated with several cardiovascular risk factors,¹² including age, smoking,²³ hypertension, diabetes mellitus, and hypercholesterolemia. Some of them (smoking and total and LDL cholesterol) were distributed equally between CAD and non-CAD patients in our study population; the others (age, height, HDL cholesterol, and presence of hypertension) were accounted for in multivariate analysis, resulting in even higher ORs. Therefore, the information provided by AIx and Tr is independent and complementary to traditional risk factors.

Vasodilating drugs like nitrates, ACE inhibitors, angiotensin II antagonists, calcium-channel blockers, and α -adrenergic blockers all decrease wave reflections and AIx.¹² All of these drugs were used much more commonly in patients with CAD in our study. If they had been withdrawn, the difference in AIx between CAD and no-CAD patients would have been even higher. On the other hand, pure β -blockers²⁴ have little or no effect on pulse wave velocity or

TABLE 3. OR of CAD According to AIx (Total Patient Group)

AIx	n	CAD (%)	Crude OR (95% CI)	Multiple-Adjusted* OR (95% CI)
Quartile 1 (-24 – -9)	73	56 (76.7)	1.00	1.00
Quartile 2 (10–21)	145	125 (86.2)	2.00 (0.97–4.11)	1.44 (0.47–4.40)
Quartile 3 (22–28)	131	117 (89.3)	2.64† (1.22–5.73)	4.13† (1.28–13.26)
Quartile 4 (29–60)	116	108 (93.1)	4.06‡ (1.72–9.57)	6.91† (1.41–33.70)
Per quartile	1.57‡ (1.18–2.08)	2.00† (1.32–3.05)

*Adjusted for age, height, hypertension (yes/no), HDL cholesterol, ACE inhibitors (yes/no), β -blockers (yes/no), nitrates (yes/no), and statins (yes/no).

† $P < 0.05$.

‡ $P < 0.01$.

TABLE 4. OR of CAD According to AIx (Younger Patient Group, up to 60 Years of Age)

Aix	N	CAD (%)	Crude OR (95% CI)	Multiple-Adjusted* OR (95% CI)
Quartile 1 (-17-9)	35	20 (57.1)	1.00	1.00
Quartile 2 (10-21)	52	37 (71.2)	1.85 (0.75-4.54)	2.21 (0.48-10.12)
Quartile 3 (22-28)	55	45 (81.8)	3.37† (1.32-8.65)	5.42† (1.08-27.06)
Quartile 4 (29-60)	48	44 (91.7)	8.25‡ (2.67-25.42)	16.81† (1.67-169.50)
Per quartile	1.95‡ (1.37-2.79)	2.49‡ (1.41-4.42)

*Adjusted for age, height, hypertension (yes/no), HDL cholesterol, ACE inhibitors (yes/no), β -blockers (yes/no), nitrates (yes/no), and statins (yes/no).
 † $P < 0.05$.
 ‡ $P < 0.01$.

wave reflections, but they enhance AIx by reduction in heart rate. We allowed for this by correcting AIx for heart rate (AIx@75), and the results were the same (Table 2).

Another major factor influencing wave reflections, and thus AIx, AP, and AIx@75, is gender. Because of the large gender differences in AIx reported previously^{25,26} and the smaller numbers of women undergoing angiography in our institution, we limited this study to men only.

The finding of the particular value of prematurely increased wave reflections for the prediction of CAD in younger patients is well in line with the fact that the impact

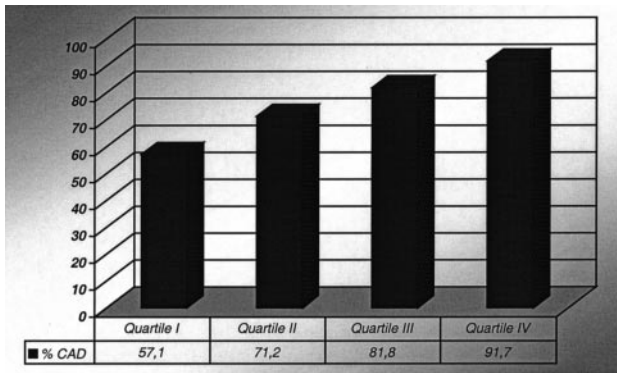


Figure 2. AIx and presence of CAD in younger patients (up to 60 years of age). AIx, -17 to 9, 10 to 21, 22 to 28, and 29 to 60 in quartiles 1, 2, 3, and 4, respectively.

TABLE 5. Severity of CAD and AIx, AP, and AIx@75 in Different Patient Groups

	Spearman's R	Level of Significance, P Value
Total patient group, n=465		
AIx and angio-score	0.06	0.18
AP and angio-score	0.12	0.01
AIx@75 and angio-score	0.09	0.05
Tr	-0.07	0.15
Younger patient group, n=190		
AIx and angio-score	0.17	0.02
AP and angio-score	0.24	0.0008
AIx@75 and angio-score	0.18	0.01
Tr	-0.17	0.02

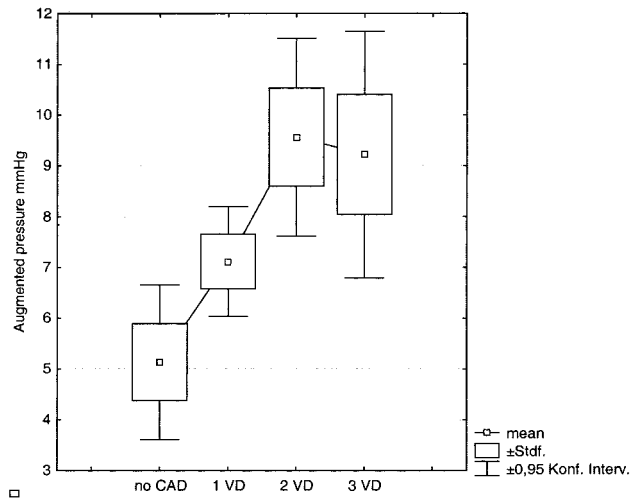


Figure 3. Severity of CAD and absolute AP in younger patients (up to 60 years of age); $P = 0.0008$ (Kruskal-Wallis ANOVA); 1, 2, and 3 VD indicates 1-, 2-, and 3-vessel disease; Stdf, standard failure; and 0,95 Konf Interv, 95% confidence interval.

of some traditional risk factors (total cholesterol and smoking)²⁷ and diagnostic tests (electron beam computed tomography²⁸) for CAD is age-related as well.

Our data are in good agreement with previous studies linking arterial stiffness²⁹ and increased wave reflections³⁰ to higher cardiovascular mortality, because the underlying disease in many of those patients was CAD. Taken together, these findings might extend the recommendation for measuring arterial wall properties in selected patients for the preventive management of cardiovascular disease to a broader spectrum of the population.³¹ With increased arterial stiffness and wave reflections, more aggressive diagnostic as well as therapeutic strategies might be appropriate, particularly in younger patients with premature stiffened arteries. However, even a reasonable therapeutic strategy based on information obtained by PWA has to be tested in a randomized controlled trial.

One potential limitation of our study is the confinement to symptomatic patients referred for coronary angiography. Thus, our findings might not be applicable to the general population.

The study of Nürnbergger et al,³² however, complements our findings; they found a strong positive correlation between

AIx and the risk of developing CAD, as assessed by the European Society of Cardiology Risk Score, in 144 asymptomatic patients without a previous history of CAD or atherosclerotic disease.

In conclusion, AIx, AIx@75, and AP, measures closely related to wave reflections and arterial stiffness, are associated with an increased risk of CAD in younger and middle-aged male patients. Those measures should serve as markers of end-organ damage regarding the arterial system, indicating an increased risk for cardiovascular complications.

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