Aortic Augmentation Index in Patients With Peripheral Arterial Disease

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Aortic augmentation index (AIx) is used to investigate arterial stiffness. The authors tested the hypothesis that patients with peripheral arterial disease (PAD) demonstrate a higher AIx and also evaluated several related factors. In 97 patients with PAD, identified by ankle-brachial pressure index (ABPI ≤0.9), and 97 controls (ABPI ≥0.91<1.4), AIx (%) was determined using tonometry of the radial artery. There was no significant difference between patients and controls in characteristics of age, sex, height, diastolic blood pressure, mean blood pressure, and heart rate. AIx was higher in patients with PAD (32±9 vs 28±9; *P*=.001). In multivariate regression analysis, AIx was independently associated with heart rate (β=−0.40, *P*=.0005). This study showed that AIx increased in patients with PAD and that heart rate is a determinant of AIx. Further studies are necessary to assess the pathophysiological and clinical importance of AIx in patients with PAD. *J Clin Hypertens (Greenwich).* 2014;16:782–787. © 2014 Wiley Periodicals, Inc.

Peripheral arterial disease (PAD) can be considered a clinical model of atherosclerosis that associates alteration in conduit and a cushioning function.[1] The first alteration depends on the diameter of the arterial lumen and can be measured using the ankle-brachial pressure index (ABPI), which represents the primary noninvasive test to identify the presence of a hemodynamically significant arterial stenosis in the lower limbs.[2] The second alteration depends on the viscoelastic properties of the arterial walls[3] and can be evaluated using a number of parameters, but they do not provide the same information.[4] We, as well as other researchers, have previously demonstrated that aortic, carotid, and femoral stiffness is increased in patients with PAD.[5,6] Pulse wave analysis (PWA) has emerged as a noninvasive and valid technique to quantify the augmentation index (AIx), considered an indicator of systemic arterial stiffness.[7] Although it has been shown that AIx is related to several risk factors for atherosclerosis,[8,9] AIx has not yet been sufficiently studied in patients with PAD. In addition, the relative importance of classical risk factors and nonpathological factors on AIx in these patients has not been well studied. This is of pathophysiological and clinical interest as AIx reflects the increase in systolic pressure induced by the reflected waves. In patients with PAD, wave reflection involved in the mechanism of systolic hypertension[1] is related with walking distance[10] and severity of PAD.[11] Finally, AIx is an independent predictor of mortality in patients with end-stage renal failure.[12] The aim of this study was to test the hypothesis that PAD could be associated with increased AIx and to investigate clinical and biochemical variables related to AIx.

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METHODS

Study Population

The study group included 194 patients recruited from the Angiology Unit, Research Center on Vascular Diseases, University of Milan L. Sacco Hospital, after receiving informed consent from each participant.

Risk Factor Assessment

Cardiovascular risk factors were ascertained by direct examination and patients were interviewed by trained research assistants. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg at the time of the visit (average of two readings) or history of hypertension or use of antihypertensive medication. Type 2 diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL or history of diabetes or use of diabetes medication (insulin or oral hypoglycemic agents). Hypercholesterolemia was defined as total serum cholesterol >200 mg/dL or by the use of statins. A history of angina or myocardial infarction (coronary artery disease [CAD]), stroke, or transient ischemic attack (cerebrovascular disease) and heart failure was also noted. The patients' exclusion criteria were the following: cardiac arrhythmias, incompressible vessels, rest pain, and coronary peripheral cerebrovascular revascularization during the past 6 months. Height and weight were measured and body mass index (BMI) was calculated as weight to height squared (kg/h²).

Assessment of Blood Pressure, ABPI, and Aortic AIx

Blood Pressure. Patients rested in a supine position for 5 minutes in a quiet room. Brachial blood pressure (BP) was measured in the dominant arm using a common sphygmomanometer. Three readings separated by

1-minute intervals were taken and the mean was used for analysis. Brachial pulse pressure (PP) was calculated as the difference between brachial SBP and DBP. Mean BP (MBP) was calculated from the formula (1/3 PP+DBP).

Ankle-Brachial Pressure Index. Systolic brachial pressure measurements to calculate the ABPI were obtained using an 8-mHz Doppler probe and a BP cuff after 10 minutes of rest with the patient in the supine position. The systolic pressure was measured from either the posterior tibial or the dorsalis pedis artery (in each leg) and was compared with the higher brachial artery pressure taken from either arm. ABPI was calculated by using the lowest value of systolic pressure of either the posterior tibial or the dorsalis pedis of each leg. PAD was defined as the presence of an ABPI $\leq$0.9.[2] The participants of the study were divided into 2 groups: 97 patients with PAD (ABPI $\leq$0.9) and 97 controls (ABPI $\geq$0.91 <1.4).

Aortic AIx . On the same day, after measuring ABPI, BP was measured with the patients in the supine position, and pulse wave analysis (PWA) of the radial artery at the wrist was performed by tonometry using a commercially available device (SphygmoCor System; AtCor Medical, West Ryde, Australia). After the acquisition of 20 to 30 reproducible sequential waveforms, the radial pulse wave was generated and a validated generalized transfer function[13] was used to derive the corresponding central aortic pressure waveform. Augmented pressure (AP) was defined as the difference between the second and the first systolic peak and was expressed in absolute terms (mm Hg). The aortic AIx was calculated as the ratio between the AP and the central PP and was expressed as percentage.[4] Time of return of the reflected wave (Tr) is the time from the beginning of the derived aortic systolic pressure waveform to the inflection point and can be used as a substitute for carotid-femoral pulse wave velocity (c-f PWV). All measurements were made by one investigator (GS) in duplicate and mean values were used for analysis. Pharmacologic treatment was suspended (when possible) 12 hours before the measurements, which took place in a comfortable environment at a temperature of 22$\pm$1°C.

Statistical Analysis

Values are expressed as mean$\pm$standard deviation and were compared with categorical variables using the χ^2 test. Differences in the mean values were compared with the two groups using Student *t* test. A *P* value <.05 was considered significant. Univariate linear regression analysis and multivariate regression models and estimating coefficient β were first built to identify variables and independent association among AIx. Coefficient of variation (R^2) was reported with a significance level of *P*<.05. Statistical analysis was conducted using SAS software (version 9.1; SAS Institute, Inc, Cary, NC).

RESULTS

The clinical characteristics of the groups are summarized in Table I. The study group consisted of 97 patients with PAD (77 men and 20 women aged 66$\pm$8 years). Among patients with PAD, 20% showed the presence of intermittent claudication (stages 1 or 2, as defined by Rutherford), 38% were current smokers, 73% had arterial hypertension, 44% had type 2 diabetes mellitus, 31% had CAD, and 3% had cerebrovascular disease. Of these, 64% of the patients were taking antihypertensive treatment (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, Ca-antagonists diuretics, and β-blockers), 69% were taking antiplatelet therapy, 41% were taking statin therapy, and 29% were taking antidiabetic therapy. The control group consisted of 97 patients (77 men and 20 women aged 65$\pm$9 years). Among these, 24% were current smokers, 47% had arterial hypertension, 35% had type 2 diabetes, and 10% had CAD. In this group, 41% were taking antihypertensive therapy, 17% were taking antiplatelet therapy, 16% were taking antidiabetic therapy, and 22% were taking statin therapy. There was no significant difference between the patients and the controls in terms of age, sex, height, body mass index, glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, uric acid, creatinine, smoking and diabetes history, DBP, MBP, and heart rate (HR). Total cholesterol and ABPI were lower in patients with PAD (*P*=.02 and *P*=.0001, respectively), in those with elevated glycated hemoglobin (*P*<.0001), and in those with a history of CAD (*P*=.0002). Hypertension (*P*<.0001) was higher in the PAD group. Differences between the groups also occurred in SBP (*P*<.001), PP (*P*<.0001), AIx (*P*=.001), AP (*P*=.0001), and Tr (*P*=.01). Differences were also found in those taking antihypertensive therapy (*P*=.0001) and in those taking antiplatelet and antidiabetic medication (*P*=.0001 and *P*=.03, respectively).

Relationship Between AIx and Other Variables

In both groups, a significant relationship in univariate analysis was found between AIx and age (β=0.34, *P*=.001), female sex (β=4.87, *P*=.03), SBP (β=0.13, *P*=.0005), PP (β=0.16, *P*=.0003), MBP (β=0.18, *P*=.008), hypertension (β=3.6, *P*=.04), statin therapy (β=6.05, *P*=.0007), and antiplatelet therapy (β=3.8, *P*=.03). A negative correlation was found with HR (β=$-$0.43, *P*=.0001), height (β=$-$0.31, *P*=.002), and lower ABPI values (β=$-$9.3, *P*=.0001). The same univariate linear regression model was developed for each group with AIx as the dependent variable. In patients with PAD, a significant relationship was found between AIx and SBP (β=0.16, *P*=.008), PP (β=0.14, *P*=.02), and MBP (β=0.29, *P*=.009), and a negative correlation was found with HR (β=$-$0.46, *P*=.0001) and glycated hemoglobin (β=$-$0.22, *P*=.05). In the control group, a negative correlation was seen between

TABLE I. Clinical Characteristics of Patients With PAD and Controls

	PAD (n=97)	Controls (n=97)	*P* Value
Age, y	66±8	65±9	ns
Men/women, No.	77/20	77/20	ns
Body height, cm	165±8	166±9	ns
Body mass index, kg/m^2	27±4	28±4	ns
Current smokers, %	38	24	ns
Hypertension, %	73	47	.0001
Diabetes type 2, %	44	35	ns
CVD history, %	3	0	ns
CAD history, %	31	10	.0002
Glycemia, mg/dL	111±38	107±25	ns
Glycated hemoglobin, %	6.9±1	6.1±0.8	.0001
Total cholesterol, mg/dL	198±42	211±37	.02
LDL cholesterol, mg/dL	126±38	135±37	ns
HDL cholesterol, mg/dL	52±16	52 ±14	ns
Triglycerides, mg/dL	126±53	133±78	ns
Acid uric, mg/dL	5.6±1	5.6±1	ns
Creatinine, mg/dL	0.8±0.1	0.9±0.1	ns
Systolic BP, mm Hg	140±22	131±20	.001
Diastolic BP, mm Hg	79±10	80±10	ns
Pulse pressure, mm Hg	61±20	50±15	.0001
Mean BP, mm Hg	100±12	99±12	ns
Heart rate, beats per min	68±11	71±12	ns
AIx, %	33±9	28±9	.001
AP, mm Hg	17±10	12±7	.0001
Tr, ms	134±11	137±11	.01
ABPI	0.7±0.1	1.1±0.1	.0001
Antihypertensives, %	64	41	.0001
Antiplatelets, %	69	17	.0001
Antidiabetics, %	29	16	.03
Statins, %	41	22	ns

Abbreviations: ABPI, ankle-brachial pressure index; AIx, augmentation index; AP, augmentation pressure; BP, blood pressure; CAD, coronary artery disease; CVD, cerebrovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant; PAD, peripheral arterial disease; Tr, time reflected wave. Continuous variables are presented as mean±standard deviation and categorical variables are presented as percentages. A *P* value <.05 was considered significant.

AIx and HR (β=−0.38, *P*=.0001), height (β=−0.33, *P*=.009), and creatinine (β=−0.17, *P*=.02), and a positive correlation was seen with statins (β=7.15, *P*=.001) (Table II). Factors that showed a significant association with AIx in the univariate analysis were entered into a multivariate regression (Table III). In both groups, a significant relationship was found between AIx and HR (β=−0.45, *P*=.0001), height (β=−0.16, *P*=.05), SBP (β=−0.44, *P*=.03), PP (β=0.28, *P*=.04), MBP (β=0.58, *P*=.002), and statin therapy (β=3.00, *P*=.02). In the same model, HR was a significant independent determinant of AIx in the PAD group (β=−0.40, *P*=.0001) and in the control group (β=−0.41, *P*=.0001), and height was associated with AIx in controls (β=−0.23, *P*=.03). Furthermore, HR explained the variability in AIx for patients with PAD (R^2=45%, *P*=.0005) and for the control group (R^2=47%, *P*=.0001).

DISCUSSION

This study examined AIx and related clinical and biochemical factors in PAD patients. The results showed that AIx was higher in patients with PAD as compared with control patients (*P*=.001) and that HR is independently associated with AIx in patients with PAD and controls (*P*=.0005 and *P*=.0001, respectively). Other authors using the same artery waveform method with the SphygmoCor device have evaluated AIx, reporting a significant increase in AIx in men with PAD.[14,15] In our study, in addition to a higher AIx, patients with PAD also exhibited a higher AP (*P*=.0001) and a lower Tr (*P*=.01), as well as increased systolic BP (*P*<.001) and PP (*P*<.0001) at the same age, sex, height, MBP, and HR with respect to controls. In this study, to evaluate the relative importance of classical risk factors and nonpathological factors on AIx, the data from all 194 patients and for each group (97 PAD and 97 controls) were used to construct a linear and multiple regression model with AIx as the dependent variable. Known or likely determinants (age, sex, height, diastolic pressure, HR) of AIx were added to the models.[16–20] Our results show that AIx is not associated with age in multivariate analysis (Table III), which is consistent with the study by McEniery and colleagues, who reported data from the Anglo-Cardiff Collaborative Trial (ACCT) demonstrating that the AIx increased in younger patients and changed less with age in older patients.[21] This lack of association with age has raised doubts about whether AIx is a valid parameter of arterial stiffness in elderly patients.[22] The other common cardiovascular risk factors associated with PAD were also shown not to be correlated with AIx. In the study by McEniery and colleagues, the associations between AIx and traditional risk factors were all more marked in younger individuals, suggesting that the impact on wave reflection is strongly dependent on age.[23] Among the variables in the regression model only HR was shown to be independently associated with AIx (*P*=.0005). This demonstrates the important role of HR in central hemodynamic parameters. An increase in HR will decrease the absolute duration of systole, shifting the reflected wave into diastole, thereby reducing AIx.[19,24] In our study, no difference was seen in HR in relation to controls, and the HR-AIx relationship was significant in the control group (*P*=.0001). Papaioannau and colleagues suggest that the inverse relationship of HR/AIx could be influenced by aortic PWV, being steeper in those with higher PWV.[25,26] A potential implication of the inverse relationship between HR/AIx is that the reduction of HR could contribute to the enhanced aortic wave reflection.[27] AIx has been used to measure the additional load imposed on the left ventricle as a result of wave reflection and correlates with left ventricular mass.[28,29] In patients with PAD, this may be counterproductive in relation to walking

TABLE II. Results of Univariate Regression Analysis for Anthropometric, Hemodynamic, Clinical, and Biochemical Parameters Using Augmentation Index as the Dependent Variable for the Total, PAD, and Controls Groups

Parameters	Total β	PAD β	Controls β
Heart rate	−0.43 (*P*<.0001)	−0.46 (*P*=.0001)	−0.38 (*P*<.0001)
SBP	0.13 (*P*=.0005)	0.16 (*P*=.008)	0.07 (*P*=.15)
PP	0.16 (*P*=.0003)	0.14 (*P*=.02)	0.12 (*P*=.05)
MBP	0.18 (*P*=.008)	0.29 (*P*=.009)	0.07 (*P*=.40)
Height	−0.31 (*P*=.002)	−0.24 (*P*=.12)	−0.33 (*P*=.009)
Age	0.34 (*P*=.001)	0.42 (*P*=.06)	0.24 (*P*=.05)
Statins	6.05 (*P*=.0007)	3.43 (*P*=.21)	7.15 (*P*=.001)
Female sex	4.87 (*P*=.03)	3.76 (*P*=.27)	5.14 (*P*=.09)
ABPI	−9.30 (*P*=.01)	1.13 (*P*=.89)	−8.02 (*P*=.38)
Hypertension	3.62 (*P*=.04)	0.04 (*P*=.98)	2.82 (*P*=.20)
Antiplatelets	3.8 (*P*=.03)	2.21 (*P*=.44)	1.67 (*P*=.57)
HDL cholesterol	0.12 (*P*=.05)	0.17 (*P*=.12)	0.13 (*P*=.09)
BMI	−0.34 (*P*=.13)	−0.33 (*P*=.41)	−0.40 (*P*=.12)
Creatinine	1.08 (*P*=.4)	−4.13 (*P*=.56)	−17.5 (*P*=.02)
Glycated hemoglobin	−0.32 (*P*=.70)	−2.22 (*P*=.046)	0.35 (*P*=.81)
Diabetes type 2	0.86 (*P*=.63)	0.02 (*P*=.99)	−1.61 (*P*=.49)
Smokers	−1.22 (*P*=.56)	−1.42 (*P*=.65)	−1.69 (*P*=.54)
CAD	1.86 (*P*=.42)	−1.51 (*P*=.59)	−0.12 (*P*=.65)
CVD	−4.63 (*P*=.51)	−7.67 (*P*=.28)	–
DBP	0.05 (*P*=.58)	0.16 (*P*=.26)	−0.01 (*P*=.86)
Triglycerides	−0.01 (*P*=.37)	0.004 (*P*=.88)	−0.01 (*P*=.24)
LDL cholesterol	−0.01 (*P*=.52)	0.05 (*P*=.16)	−0.04 (*P*=.19)
Glycemia	−0.02 (*P*=.36)	−0.06 (*P*=.05)	0.0001 (*P*=.99)
Uric acid	−0.16 (*P*=.46)	−0.45 (*P*=.63)	−0.11 (*P*=.61)
Antidiabetics	4.10 (*P*=.07)	1.10 (*P*=.07)	5.11 (*P*=.12)
Antihypertensives	2.18 (*P*=.23)	4.15 (*P*=.14)	−4.20 (*P*=.14)

Abbreviations: ABPI, ankle-brachial pressure index; BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MBP, mean blood pressure; PAD, peripheral arterial disease; PP, pulse pressure; SBP, systolic blood pressure. Values are expressed as coefficients (β) and *P* values.

TABLE III. Results of Multiple Regression Analysis Using Augmentation Index as the Dependent Variable for the Total, PAD, and Controls Groups

Parameters	Total β	PAD β	Controls β
Heart rate	−0.45 (*P*=.0001)	−0.40 (*P*=.0005)	−0.41 (*P*=.0001)
Height	−0.16 (*P*=.05)	–	−0.23 (*P*=.03)
SBP	−0.44 (*P*=.03)	−0.22 (*P*=.61)	–
PP	0.28 (*P*=.04)	0.19 (*P*=.50)	–
MBP	0.58 (*P*=.002)	0.38 (*P*=.35)	–
Creatinine	–	–	−0.86 (*P*=.12)
Statins	3.00 (*P*=.02)	–	3.43 (*P*=.06)

Abbreviations: MBP, mean blood pressure; PAD, peripheral arterial disease; PP, pulse pressure; SBP, systolic blood pressure. Values are expressed as coefficients (β) and *P* values.

ability since a higher AIx was associated with a shorter walking distance.[10,30]

The mechanisms whereby PAD is associated with increased Aix remain unknown; however, several mechanisms are plausible. The pressure wave reflection responsible for aortic augmentation arises mainly from the lower body, particularly from the lower extremities. AIx depends on the amount of reflection determined by arterial tone at the major sites of reflection and on the timing of reflected waves determined by stiffness in the aorta and large arteries.[3] In healthy individuals, a decline in endothelial function is associated with increased wave reflections.[31] Endothelial dysfunction is recognized as one of the earliest events of atherogenesis and is an important step in the progression of atherosclerosis, including PAD.[32] A population-based study reported a relationship between ABPI, AP, and AIx, suggesting that the presence of PAD may increase wave reflection or vice versa, while an increase in arterial stiffness and wave reflection may increase the risk of developing PAD.[33] In other words, it is possible that in patients with PAD, arterial obstructions and an increase in vasomotor tone of muscular arteries of the lower limbs as a result of a lower bioavailability of nitric oxide, may have caused a significant increase in AP and AIx.[34] Additionally, since the nature of reflected waves depends on the elastic properties of the entire arterial tree, changes in aortic distensibility can have profound effects on the aortic pressure wave.[35] Thus, the increase of PWV in PAD may have increased the pulse wave propagation resulting in an early return of wave reflections. In previous works, the effects of height on wave of reflection parameters have been shown.[17,20] In our study, patients with PAD showed different timing of wave reflection (Tr), but this could not have been influenced by height (ie, not different between the two groups) while the height is not related to Aix. Safar and colleagues suggest that in patients with PAD with arterial lesions in the lower limbs, the terminal aorta may be a major site of wave reflection.[1] Therefore, the Tr reduction in PAD could be caused by a shorter effective length of the arterial system or the result of an increase in c-f PWV. The increase of PWV in the PAD may have increased the pulse wave propagation with a consequent early return of wave reflection. Thus, in patients with PAD with arterial stiffness,[5] the reflected waves return to the central arteries during late systole, adding to the forward wave and increasing systolic pressure.[1,3,36] This is compatible with our results that show the different BP pattern in PAD patients compared with control patients (Table I). These observations suggest that AIx can be affected by phenomena (arteriosclerosis and atherosclerosis) that, although considered different pathological entities,[37] both tend to coexist in older patients. The Rotterdam Study, a population-based investigation, showed that an increase

in arterial stiffness is associated with atherosclerosis in different arterial districts.[38] Atherosclerosis leads to thick, stiff arterial walls, calcification, and plaque formation, which would change the mechanical properties of the arteries.[6] Arteriosclerosis and atherosclerosis share, over time, the integrated effects of established vascular risk factors such as age, hypertension, and diabetes and can develop concomitantly.

Study Limitations

There are limitations to this study, including its cross-sectional nature, which precludes conclusions regarding the cause-effect relationship between HR and AIx. In this study, medications used are likely to have had some influence on the behavior of the pulse wave. The 12-hour period without treatment may not have been sufficient in the case of drugs whose pharmacokinetics extends beyond this period. The AIx has been reported to be different between men and women, therefore a more detailed profile of patients with PAD may be required to assess predictors of AIx in these patients.

CONCLUSIONS

Although there is still discussion regarding the validity of AIx as a parameter of arterial stiffness in elderly patients, this study shows that PAD is characterized by an increase in AIx at the same age, sex, height, diastolic, MBP, and HR with respect to controls. In patients with PAD, larger values of AIx could indicate a reduction in the reservoir function compliance properties of the aorta and/or increased wave reflection from the periphery. Further studies are necessary to assess pathophysiological and clinical implications of AIx in PAD patients.

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