Increased Aortic Stiffness and Related Factors in Patients With Peripheral Arterial Disease

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A number of conditions have been associated with functional changes of large arteries. The aim of this study was to evaluate the factors associated with aortic stiffness in patients with peripheral arterial disease (PAD). The authors studied 86 patients with PAD (ankle-brachial pressure index [ABPI] ≤0.9) and 86 controls. Aortic stiffness was determined by pulse wave velocity (aPWV) using applanation tonometry. In PAD patients, aPWV was higher compared with controls (11±3 vs 9.8±1.8; *P*=.002). In multiple regression analysis, aPWV was independently associated with pulse pressure (β=0.05, *P*=.01) in the PAD patients and with age in the control group (β=0.08, *P*=.0005). The results of this study confirm an aPWV increase in patients with PAD and emphasize the association between blood pressure and aPWV. Further studies are necessary to assess whether higher aortic stiffening adds prognostic value to ABPI, which is the most powerful prognostic indicator in PAD. *J Clin Hypertens (Greenwich).* 2013;15:712–716. ©2013 Wiley Periodicals, Inc.

Patients with peripheral arterial disease (PAD) often have cardiovascular risk factors such as diabetes mellitus, smoking, and systemic hypertension, and these conditions are associated with increased aortic stiffness.[1–3] However, aortic stiffness has not received much attention in patients with PAD[4] and the relative importance of classical risk factors and nonpathological factors[5–7] on arterial stiffness in these patients has not been well studied. This is of clinical relevance because aortic stiffening (increased aortic pulse wave velocity [aPWV]) is considered a new cardiovascular risk factor.[8] Arterial stiffening reduces the buffering capacity of the main elastic arteries, which leads to increased systolic and pulse pressure, promotes left ventricular hypertrophy and dysfunction, and impairs capacity for myocardial perfusion.[9] It is an independent predictor of all-cause and cardiovascular death in high-risk patients[10] and, in PAD patients, an association between arterial stiffness and exercise performance has also been noted.[11,12] The aim of our study was to compare aPWV in PAD patients and controls and investigate the predictors of aPWV.

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METHODS

Study Population

The study group included 172 patients (age range, 40–89 years) recruited from the angiology unit of the Research Center on Vascular Diseases at the University of Milan L. Sacco Hospital after receiving informed consent from each participant.

Risk Factors Assessment

Cardiovascular risk factors were ascertained through direct examination and interview 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 (mean of two readings) or history of hypertension or use of antihypertensive medications (diuretics, β-blockers, angiotensin-converting enzyme inhibitors, AT_2-blockers or Ca-antagonists). Type 2 diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL or history of diabetes or of use of diabetes medications (insulin or oral hypoglycemic agents). Hypercholesterolemia was defined as total serum cholesterol >200 mg/dL or of the use of lipid-lowering treatment. A history of angina or myocardial infarction (coronary artery disease [CAD]), stroke or transient ischemic attack (cerebrovascular disease [CVD]), and heart failure were also noted. The patients' exclusion criteria were the following: coronary revascularization or cerebrovascular events during the past 6 months, previous revascularization procedures of the lower limb, cardiac arrhythmias. All women were in the postmenopausal stage and none were taking hormonal medication. Height and weight were measured and body mass index was calculated as weight to height squared (kg/h²).

Assessment of Hemodynamics and Arterial Stiffness

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. Peripheral pulse pressure (PP) was calculated as the difference between brachial systolic BP (SBP) and diastolic BP (DBP). Mean BP (MBP) was calculated from the formula (1/3 PP+DBP).

Aortic Pulse Wave Velocity. aPWV was measured by sequentially recording electrocardiography (ECG)-gated carotid and femoral artery waveforms. Wave transit time was calculated by software using the R wave of a simultaneously recorded ECG as a reference frame (SphygmoCor; AtCor Medical, Sydney, Australia). The distance between the carotid and the femoral sampling sites was measured above the surface of the body with a tape. aPWV was determined by dividing the distance between the two recording sites by the wave transit time.[13] All measurements were made 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±1°C.

In studies performed on two separate days in 19 PAD patients by a single operator, the within-patient coefficient of variation (CV) of aPWV was 5.05%.

Ankle-Brachial Pressure Index. BP measurements for calculation of the ankle-brachial pressure index (ABPI) were obtained using a 8-mHz Doppler probe and a BP cuff after 10 minutes of rest with the patient in a supine position. The systolic pressure was measured from either the posterior tibial and dorsalis pedis artery (in each leg) and was compared with the higher brachial artery pressure taken from either arm. PAD was defined as the presence of an ABPI ≤0.9.[14] The participants of the study were divided into two groups: 86 patients with PAD (ABPI ≤0.9) and 86 controls (ABPI ≥0.91).

Statistical Analysis

Values are expressed as mean±standard deviation, and were compared with categorical variables using chi-square test. Differences in the mean values were compared with the two groups using *t* test. A *P* value of <.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 aPWV. R^2 values were reported for model with a significance level of <.05.

RESULTS

The clinical characteristics of the groups are summarized in Table I. The study group consisted of 86 patients with PAD (71 men, 15 women), aged 66±8 years. Among PAD patients, 23% with intermittent claudication (stage II, as defined by Fontaine), 30% had a history of smoking, 30% had a history of smoking, 77% had arterial hypertension, 43% had type 2 diabetes mellitus, 26% had CAD, and 3% had CVD. Of these, 58% of the patients were taking antihypertensive treatment, 28% were taking antidiabetic medication, 64% were taking antiplatelet therapy, and 44% were taking statin therapy. The control group consisted of 86 patients (71 men, 15 women), aged 65±9 years. Among these, 19% had a history of smoking, 44% had arterial hypertension, 33% had type 2 diabetes mellitus, and 7% had CAD. In this group, 35% were taking antihypertensive therapy, 15% were taking antidiabetic treatment, 19% were taking antiplatelet therapy, and 21% were taking statin therapy. There was no significant difference between the patients and the controls in age, sex, height, body mass index, glucose, high-density lipoprotein, low-density lipoprotein cholesterol, triglycerides, uric acid, creatinine,

TABLE I. Clinical Characteristics of PAD and Controls

	PAD (n=86)	Controls (n=86)	*P* Value
Age, y	66±8	65±9	ns
Men/women, No.	71/15	71/15	ns
Body height, cm	165±8	166±9	ns
Body mass index, kg/m^2	27±4	28±4	ns
Smoking history, %	30	19	ns
Hypertension, %	77	44	.0001
Diabetes, type 2, %	43	33	ns
CVD history, %	3	0	ns
CAD history, %	26	7	.0002
Glycemia, mg/dL	112±38	106±24	ns
Hemoglobin A_{1c}, %	7±1	6±0.7	.0001
Total cholesterol, mg/dL	193±44	209±37	.02
LDL, mg/dL	124±39	133±38	ns
HDL, mg/dL	51±16	52±14	ns
Triglycerides, mg/dL	124±51	127±78	ns
Uric acid, mg/dL	5.6±1	5.6±1	ns
Creatinine	0.8±0.1	0.9±0.1	ns
Systolic blood pressure, mm Hg	142±21	132±20	.001
Diastolic blood pressure, mm Hg	79±10	80±10	ns
Pulse pressure, mm Hg	62±20	51±16	.0001
Mean blood pressure, mm Hg	101±12	98±13	ns
Heart rate, beats per min	68±11	71±12	ns
Pulse wave velocity, m/s	11±3	9.8±1.8	.002
ABPI	0.7±0.1	1.1±0.1	.0001
Antihypertensives, %	57	35	.0001
Antidiabetics, %	28	15	.03
Antiplatelets, %	64	19	.0001
Statins, %	44	21	ns

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

smoking and diabetes history, DBP, MBP, and heart rate. Total cholesterol and ABPI were lower in patients with PAD (P=.02; P=.0001). Glycate hemoglobin A_{1c} (HbA_{1c}) (P<.0001) and history of CAD (P=.0002) and hypertension (P<.0001) were higher in the PAD group. Differences between the groups also occurred in SBP (P<.001), PP (P<.0001), and aPWV (P<.002). Differences were also found in antihypertensive therapy (P=.0001), antidiabetic therapy (P=.03), and antiplatelet medication (P=.0001).

Relationship Between aPWV and Other Variables

In both groups, a significant relationship was found in the univariate analysis between aPWV and age (β=0.11, P=.0001), SBP (β=0.04, P=.0001), PP (β=0.05, P=.0001), MBP (β=0.04, P=.01), hypertension (β=1.36, P=.003), type 2 diabetes mellitus (β=1.02, P=.02), HbA_{1c} (β=0.73, P=.0009), and antihypertension (r=0.98, P=.04), and a negative correlation was found with ABPI (β=−3.9, P=.0001) (Table II). In the PAD group, aPWV was correlated with PP (β=0.05, P=.01) and marginally with age (β=0.13, P=.06). In the control group, aPWV was correlated with age (β=0.07, P=.0004), SBP (β=0.03, P=.0002), PP (β=0.04, P=.0004), MBP (β=0.04, P=.001), and arterial hypertension (β=0.86, P=.03).

In the multiple regression model, aPWV was independently associated with PP only (β=0.05, P=.01) and with age for the patient group (β=0.13, P=.06), whereas a significant independent association of PWV occurred with age in the control group (β=0.08, P=.0005) (Table III).

TABLE II. Results of Univariate Regression Analysis for Anthropometric, Hemodynamic, Clinical, and Biochemical Parameters Using Pulse Wave Velocity as the Dependent Variable for the Total Population

Parameters	Total (β)	PAD (β)	Controls (β)
PP	0.05 (P=.0001)	0.05 (P=.01)	0.04 (P=.0004)
Age	0.11 (P=.0001)	0.13 (P=.06)	0.07 (P=.0004)
SBP	0.04 (P=.0001)	0.03 (P=.10)	0.03 (P=.0002)
MBP	0.04 (P=.01)	0.003 (P=.92)	0.04 (P=.001)
ABPI	−3.9 (P=.0001)	−3.88 (P=.17)	0.20 (P=.90)
Hypertension	1.36 (P=.003)	0.33 (P=.77)	0.86 (P=.03)
Diabetes mellitus, type 2	1.02 (P=.02)	1.19 (P=.23)	−0.06 (P=.87)
Hemoglobin A_{1c}	0.73 (P=.0009)	0.63 (P=.07)	0.16 (P=.55)
Antihypertension	0.98 (P=.04)	−0.03 (P=.97)	0.43 (P=.40)
Heart rate	0.007 (P=.71)	0.05 (P=.22)	0.004 (P=.82)
DBP	−0.005 (P=.80)	0.06 (P=.14)	0.03 (P=.09)
BMI	0.10 (P=.08)	0.17 (P=.19)	0.05 (P=.28)

Abbreviations: ABPI, ankle-brachial pressure index; BMI, body mass index; DBP, diastolic blood pressure; MBP, mean blood pressure; PAD, peripheral arterial disease; PP, pulse pressure; SBP, systolic blood pressure.

TABLE III. Results of the Multiple Regression Analysis Using Pulse Wave Velocity as the Dependent Variable for Each Group (PAD and Controls)

Parameters	Total (β)	PAD (β)	Controls (β)
PP	0.06 (P=.23)	0.05 (P=.01)	0.02 (P=.61)
Age	0.06 (P=.02)	0.13 (P=.07)	0.08 (P=.0005)
MBP	−0.007 (P=.91)	0.003 (P=.92)	0.02 (P=.63)

Abbreviations: MBP, mean blood pressure; PAD, peripheral arterial disease; PP, pulse pressure.

Furthermore, PP explained (R^2=11.8%, P=.01) the variability in aPWV for PAD patients and age explained (R^2=15.8%, P=.0004) the variability in aPWV for the control group.

DISCUSSION

This study examined arterial stiffness and related factors in PAD patients. The results revealed that aortic stiffness as assessed by aPWV was higher in PAD patients as compared with control patients (P=.002) and that aPWV was independently associated with PP (P=.01).

Zagura and colleagues[15] and Kals and colleagues[16] recently reported a significant association between PAD and aPWV using the same carotid-femoral artery waveforms method with the SphygmoCor (AtCor Medical) device. In our study, in addition to a higher aPWV, patients with PAD also exhibited a higher PP (P=.0001). Although PP and aPWV are correlated, they represent two aspects of hemodynamics.[17]

aPWV is an integrative marker of arterial function, whereas PP is viewed as a surrogate marker of stiffness potentially confounded by factors related to cardiac function such as heart rate, stroke volume, pattern of ventricular ejection, and timing and intensity of wave reflections.[18]

Increased aortic stiffness is an intermediate endpoint for cardiovascular events, independently of and beyond peripheral PP. aPWV has been associated with various factors such as age, BP, and heart rate.

In our study, the data from all 172 patients were used to construct a linear and multiple regression model with aPWV as the dependent variable. Known or likely determinants of aPWV were added to the models.[5–7] The results of multiple regression analysis (Table III) indicated that PP only was significantly correlated with aPWV (P=.01), which reflects the sclerotic changes of the aortic vessel wall. The results also indicate that the changes in aPWV in PAD patients could be explained in terms of PP. One possible explanation of this relationship is that arterial stiffening may be caused by the fracture of load-bearing elastic lamellae and degeneration of the arterial wall as a result of cyclic stress[19] or permanent BP elevation, independently of MBP.[20] These findings are consistent with data on type 2 diabetes by Smith and colleagues[21] and with the idea that more

pronounced aortic stiffening is responsible for the different BP pattern observed in PAD patients compared with control patients.[22]

We also found no significant relationship of aPWV with other cardiovascular risk factors (diabetes mellitus, smoking), which is consistent with a recent systematic review concerning aPWV and cardiovascular risk factors.[23] In PAD patients, aortic stiffness may be locally exacerbated by atherosclerosis, which is a systemic chronic inflammatory disease.[24] Biomarkers of inflammation are positively associated with PAD and with the parameters of arterial stiffness (aPWV, PP).[25–27] In other words, inflammatory, high-grade oxidative stress and calcification processes within the vessel wall (as part of vascular remodeling) can modulate arterial stiffness (Figure).[28] Kals and colleagues demonstrated that elevated plasma β_2-microglobulin ($\beta 2\mu$) levels were associated with higher aortic stiffness irrespective of cardiovascular disease risk factors, suggesting that $\beta 2\mu$ may influence the pathogenesis of aortic stiffness in atherosclerosis. Clancy and colleagues[29] recently reported an association between serum levels of osteoprotegerin (OPG) and infrarenal abdominal aorta calcification in patients with PAD. In the article by Zagura and colleagues, OPG levels were independently associated with increased aPWV in PAD patients and controls. This association remained significant after the correction of confounding factors (BP levels, pharmacologic therapy, and cardiovascular risk factors).

Potential Pathophysiologic Implications

In PAD patients, a less distensible aorta cannot efficiently accommodate the blood volume ejected by the left ventricle, which results in high systolic pressure and PP. These hemodynamic modifications may influence ventricular afterload and microcirculation function.[30] Among PAD patients, increased PP and higher aortic augmentation index, a measure of arterial wave reflection that is affected by arterial stiffness, are associated with impaired walking ability and vascular bed reserve.[31]

A reduction of aPWV by an angiotensin-converting enzyme inhibitor has been shown to improve performance, suggesting aortic stiffness as a potential target of intervention.[32] However, further studies are needed to understand the relationship between arterial stiffness and functional performance in PAD patients.

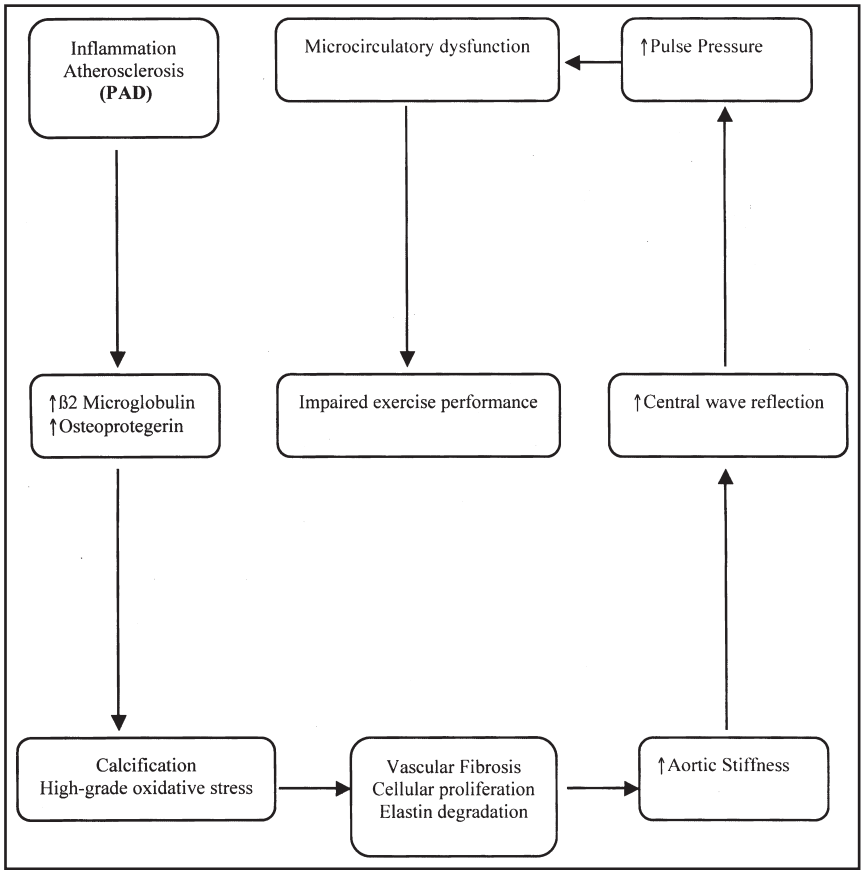

FIGURE. Potential pathophysiologic mechanisms and microcirculation implications for aortic stiffness in patients with peripheral arterial disease (PAD).

Study Limitations

The present study has some limitations. First, this was an observational study that could not reveal causal relationships between PAD and aortic stiffening and between PP and aPWV. Future long-term longitudinal studies, preferably starting in young and normotensive patients, will be needed to elucidate these issues. Second, the regression model could only predict a part of the variability of aPWV (R^2=11.8%, P=.01), indicating that other factors (such as inflammation and calcification) not currently studied may play an important role in aortic stiffness in PAD patients.

CONCLUSIONS

This study demonstrates that PAD is characterized by an increase in aortic stiffness at the same age, sex, MBP, and heart rate in respect to controls. In these patients, the contribution of cardiovascular risk factors on aortic stiffening appears to be insignificant. Our results focus attention on the major role of PP in determining aortic stiffening in PAD patients. Thus, excessive aortic stiffness and increased PP contribute to damage of the arterial wall and may represent both a cause and a consequence of atherogenesis. In PAD patients, the prognostic usefulness of ABPI measurement is well defined but the exact role of aPWV in this regard is not clear. The independence of aPWV from cardiovascular risk factors and lower ABPI increases the potential for aortic stiffness measurements to contribute to cardiovascular risk stratification in PAD.

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