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Aortic Pulse Wave Velocity as a Marker of Atherosclerosis in Hypertension

Increased aortic pulse wave velocity (PWV), an index of arterial stiffness, has been proposed as a marker of atherosclerosis in subjects with hypertension. Whether PWV reflects the extent and/or the topography of the lesions has never been investigated. In a cohort of 299 subjects treated for essential hypertension, 92 patients presented with documented vascular diseases, including coronary heart disease, peripheral vascular disease (lower limbs), cerebrovascular accidents, and abdominal aortic aneurysm, as evidenced by the presence of clinical events. PWV was obtained with an automated, noninvasive device with a repeatability coefficient of over 0.90. PWV was higher in patients with documented vascular diseases (15±4 vs. 13±3 m/sec, respectively; $p<0.01$) than in patients without, even after adjustments for age, gender, mean blood pressure, plasma glucose, and plasma creatinine. After adjustment for age and blood pressure, PWV was strongly ($p<0.001$) associated only with the presence of documented vascular disease of the lower limbs and abdominal aorta, or both. PWV was significantly associated with documented coronary and cerebrovascular disease, but only on univariate analysis. This study provides evidence that increased aortic PWV is strongly associated with the presence and extent of clinical atherosclerosis, but mainly in specific arterial territories, such as the abdominal aorta and the lower limbs. (CVR&R. 2001;22:420–425,431)
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Hypertension is a well recognized cardiovascular (CV) risk factor.[1] Interventional studies in hypertensive populations have demonstrated the significant decrease in CV events obtained with antihypertensive drug treatment.[2] Nevertheless, in these studies, the number of patients required to be treated in order to avoid one CV event has been high.[3] Because CV events affect mainly large arteries, consideration of other CV risk factors acting on conduit vessels is important in evaluating individual risk, risk stratification, and cost-effective preventive therapy.[4] This is particularly important to consider in treated hypertensive patients, in whom the extent of atherosclerosis increases in relation to the prolongation of life and the duration of treatment.

Aortic stiffness increases with age[5,6] and hypertension,[7] and is also enhanced in subjects with diabetes mellitus[8] and end-stage renal disease.[9,10] Increased aortic stiffness is associated with coronary ischemic disease and has been proposed to be a marker of atherosclerosis.[11–13] However, whereas in subjects with hypertension, increased aortic stiffness reflects diffuse alterations affecting both central and peripheral arteries, atherosclerosis involves more

tories, particularly arterial bifurcations. Whether increased aortic stiffness is associated with specific arterial site alterations has never been investigated in atherosclerotic subjects with hypertension.

The purposes of the present study were: 1) to test the ability of aortic pulse wave velocity (PWV), a classic marker of aortic stiffness, to serve as an indicator of atherosclerotic vascular damage in treated hypertensive subjects; and 2) to identify the atherosclerotic alterations that are specifically associated with increased PWV.

Materials and Methods

Study Cohort. From January, 1996–January, 1997, 980 patients entered the Department of Internal Medicine of Broussais Hospital for an evaluation of one or more CV risk factors, including smoking, dyslipidemia, diabetes mellitus, family history of premature CV events, and/or high blood pressure, with or without previously documented vascular diseases (DVD) (Table I). Of the 980 patients, only subjects chronically treated (>1 year) for essential hypertension were selected. Patients were included regardless of whether or not blood pressure was well controlled (systolic blood pressure of <140 mm Hg and diastolic blood pressure of <90 mm Hg). Patients with secondary hypertension, cancer, insulin-dependent diabetes, or severe renal insufficiency (plasma creatinine of >300 μmol/L) were excluded from the study. The cohort was composed of 299 treated (Table I) hypertensive patients (176 males, 123 females), with a mean age (±SD) of 62±13 years. Each subject provided informed consent for the study, which was approved by our institutional review board.

Information compiled from the questionnaire filled out at entry included gender, age, weight and height, family history of CV events, personal history of diabetes mellitus and/or dyslipidemia, smoking habits, and use of medications, including antihypertensive drugs. According to the clinical questionnaire and findings on examination during hospitalization, DVD was absent in 207 patients (Group I) and present in 92 patients (Group II). For determination of DVD in hypertensive patients, the following criteria were used, in accordance with the International Classification of Diseases (ninth revision): 1) coronary heart disease was defined as a history of angina pectoris (pericardial chest pain precipitated by exertion and relieved by rest or nitrates) confirmed by coronary angiography; myocardial infarction (MI) according to the medical history and records or the finding of typical sequelae of infarction on electrocardiography (EKG); coronary artery bypass surgery; or percutaneous transluminal angioplasty. 2) Cerebrovascular disease was defined as a history of transient ischemic attacks or thrombotic stroke verified by computed tomography, without evidence of embolic cardiopathy; severe carotid artery stenosis (>70%) verified by Doppler echography and treated angiographically or surgically. 3) Peripheral vascular disease was defined as typical symptoms of lower limb vascular disease of major arteries, including the renal and splanchnic circulation, and this diagnosis was given to those who had undergone surgery or percutaneous transluminal angioplasty for this disorder. 4) The presence of abdominal aortic aneurysm was assessed by Doppler echography or computed tomography and was applied to those who

TABLE I. DRUG THERAPY OF HYPERTENSION AND OTHER CARDIOVASCULAR DISEASES IN GROUPS I AND II

	Group I (N=207)	Group II (N=92)
Diuretics	28	39
Angiotensin-converting enzyme inhibitors	28	36
Calcium antagonists	39	53
β Blockers	27	36
Central antihypertensive drugs	9	12
α Blockers	4	2
Angiotensin II antagonists	1	1
Nonsteroidal anti-inflammatory drugs	1	8
Nitrates	1	9
Acetylsalicylic acid	4	35
Arterial vasodilators	1	10
Cholesterol-lowering agents	11	17
Antidiabetics	4	21

Note that nonsteroidal anti-inflammatory drugs, nitrates, acetylsalicylic acid, arterial vasodilators, cholesterol-lowering agents, and antidiabetics were used significantly more frequently ($p<0.02$) in Group II than in Group I.

TABLE II. SITE OF ATHEROSCLEROTIC ALTERATIONS

	GROUP I (N=207)	GROUP II (N=92)
Coronary arteries (%)	0	70±0.5*
Lower limb arteries (%)	0	20±0.4*
Abdominal aorta (%)	0	20±0.4*
Carotid-cerebral arteries (%)	0	30±0.5*

Values are means±1 SD.
*$p<0.001$

had undergone surgery for this disorder. Drug treatments for hypertension and other cardiovascular diseases are listed in Table I. The extent of atherosclerosis was assessed as the number of vascular sites involved by DVD. The sites of DVD are listed in Table II.

Methods

Measurements were obtained in the morning after an overnight fast with patients in the supine position. Brachial blood pressure was measured with a mercury sphygmomanometer after 15 minutes of rest. Phases I and V of the Korotkoff sounds were regarded, respectively, as systolic blood pressure (SBP) and diastolic blood pressure (DBP). The mean blood pressure (MBP) was calculated as: MBP=DBP+(SBP - DBP/3). Five measurements obtained 2 minutes apart were averaged. Plasma obtained by venous puncture was separated without delay at 4°C in a refrigerated centrifuge and stored at 4°C until analysis (determination of routine chemistry profile by standard methods). Total cholesterol and triglycerides were determined by a Technicon Chem™ assay (Technicon Instruments, Tarrytown, NY), and high-density lipoprotein (HDL) cholesterol was measured in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with heparin-manganese chloride.

After blood pressure determination, the PWV measurement was performed, before the three-lead orthogonal EKG and blood sampling, in a controlled environment at 22±2°C. The aortic PWV was determined with an automated device, the Complior™ (Colson, Garges les Gonesses, France), which allows online pulse wave recording and automatic calculation of PWV.[14] Briefly, common carotid artery and femoral artery pressure waveforms were recorded noninvasively with a TY-306-Fukuda™ pressure-sensitive transducer (Fukuda, Tokyo, Japan). The pressure waveforms were digitized at the sample acquisition frequency of 500 Hz. The two pressure waveforms were then stored in a memory buffer. A preprocessing system automatically analyzed the gain in each waveform and adjusted it for equality of the two signals. Details of this procedure have been previously published.[14] When the operator observed a pulse waveform of sufficient quality on the computer screen, digitization was suspended and calculation of the time delay between the two pressure upstrokes was initiated. Measurement was repeated over at least 10 different cardiac cycles and the mean was used for the final analysis. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites (D), while pulse transit time (t) was automatically determined by the Complior™; PWV was automatically calculated as PWV=D/t. The validation of this automated method and its reproducibility have been previously described;[14] the intraobserver repeatability coefficient is 0.935 and the interobserver reproducibility coefficient is 0.890.

For the statistical evaluation, STATISTICA® (version 4.5, StatSoft, Tulsa, OK, 1993) was used. The values presented are means±1 standard deviation. Multiple regression analysis was performed in a forward, stepwise fashion. Means were compared with ANOVA. Covariates were considered when necessary. A p value of ≤ 0.05 was considered significant.

Results

Mean Values. Table III shows that, at the same mean arterial pressure, subjects in Group II had a lower DBP ($p<0.05$) and a higher SBP ($p<0.05$) and pulse pressure ($p<0.001$) than those in Group I. PWV (m/sec) was markedly higher in Group II than in Group I: 15±4 vs. 13±3 ($p<0.001$).

As Table IV indicates, significantly higher values were observed in Group II for: age ($p<0.001$), tobacco consumption ($p<0.001$), plasma creatinine ($p<0.001$), plasma glucose, potassium, and uric acid ($p<0.01$), and triglycerides ($p<0.05$). Plasma cholesterol and HDL cholesterol did not differ significantly.

Factors Influencing Aortic PWV. Table V shows that, in addition to age and mean arterial pressure, PWV was influenced by the presence of DVD, but exclusively

TABLE III. BLOOD PRESSURE AND PULSE WAVE VELOCITY

	Group I (N=207)	Group II (N=92)
Systolic arterial pressure (mm Hg)	143±19	148±20*
Diastolic arterial pressure (mm Hg)	84±12	80±12*
Mean arterial pressure (mm Hg)	103±13	103±13
Pulse pressure (mm Hg)	59±15	68±18**
Heart rate (beats/min)	69±10	66±10*
PWV (m/sec)	13±3	15±4**

Values are means±1 SD.
*$p<0.05$; **$p<0.001$

TABLE IV. CLINICAL AND BIOLOGIC CHARACTERISTICS

	Group I (N=207)	Group II (N=92)
Sex (male/female)	115/92	61/31*
Age (years)	57±13	68±12***
Body mass index (kg/m²)	27.3±4.4	27.0±4.5
Familial history of CV event	1.0±1.0	0.7±0.9*
Tobacco consumption (number packs/year)	8.1±14.5	17.0±21.0***
Plasma creatinine (μmol/L)	89±19	111±32***
Plasma glucose (mmol/L).	5.9±1.5	6.6±2.1**
Plasma potassium (mmol/L)	4.2±0.4	4.3±0.5**
Plasma uric acid (μmol/L)	338±89	382±95**
Plasma triglycerides (mmol/L)	1.2±0.7	1.4±0.8*
Plasma total cholesterol (mmol/L)	5.7±1.1	5.7±1.2
Plasma HDL cholesterol (mmol/L)	1.3±0.4	1.2±0.4

Values are means±1 SD. HDL=high-density lipoprotein; CV=cardiovascular
*$p<0.05$; **$p<0.01$; ***$p<0.001$

from two different sites: the lower limbs ($p<0.001$) and the abdominal aorta ($p=0.009$). PWV was significantly ($p<0.001$) associated with coronary and cerebrovascular DVD but only on univariate analysis.

After adjustment for age and mean arterial pressure, PWV was significantly elevated ($p<0.005$) at the lower limbs and the abdominal aorta, and much more dramatically so when alterations were observed at these sites (Table VI).

Factors Influencing Brachial Pulse Pressure. Brachial pulse pressure was influenced by only two factors: age ($p<0.001$) and mean arterial pressure ($p<0.001$) ($F=62.05$; $r^2=0.351$) (Table VII). After adjustment for these two variables, brachial pulse pressure remained elevated in Group II, but this elevation was associated with only two sites of DVD: the lower limbs and cerebrovascular areas. Brachial pulse pressure was even higher when the two sites were combined (Table VIII).

TABLE V. MULTIPLE REGRESSION ANALYSIS OF PWV

Multiple Regression			Aortic PWV (m/sec)	
Variable	ß Coefficient	Multiple R Square	T (294)	P Value
Age (years)	0.468	0.256	9.659	<0.001
MAP (mm Hg)	0.203	0.304	4.315	<0.001
Lower limbs site	0.189	0.343	3.936	<0.001
Aortic site	0.125	0.358	2.628	0.009

$F=41.162$; $R^2=0.358$; MAP=mean arterial pressure; PWV=pulse wave velocity

TABLE VI. PWV AFTER ADJUSTMENT FOR AGE AND MAP

	PWV (M/SEC)	AGE (YEARS)	MAP (MM HG)	ADJUSTED PWV (M/SEC)
No site	12.8	59	103	13.8
Lower limb site	16.4	71	105	15.8
Aortic site	15.4	70	103	15.1
Lower limb and aortic sites	19.3	66	107	19.2

Values are means. PWV was significantly different between "no site" and the three other groups ($p=0.001$; Scheffé test). MAP=mean arterial pressure; PWV=pulse wave velocity

TABLE VII. MULTIPLE REGRESSION ANALYSIS OF BRACHIAL PULSE PRESSURE

VARIABLE	ß COEFFICIENT	MULTIPLE R SQUARE	T (270)	P VALUE
Age (years)	0.449	0.168	8.866	<0.001
MAP (mm Hg)	0.384	0.351	7.599	<0.001

$F=62.05$; $R^2=0.351$; MAP=mean arterial pressure

In the multiple regression analysis related to factors influencing either PWV or pulse pressure, we found no significant association with body mass index, family history of CV events, tobacco consumption, or levels of plasma creatinine, glucose, potassium, uric acid, or total or HDL cholesterol. The presence of drug therapy for hypertension did not influence the multiple regression analysis.

Discussion

The salient findings of this study were that, in a population of subjects treated for hypertension, aortic PWV was strongly and independently related to the presence and extent of DVD, and the increase in PWV was independently associated with DVD in some vascular territories, such as the lower limbs and the abdominal aorta. PWV was significantly associated with coronary and cerebrovascular DVD, but only on univariate analysis.

In this study, we used PWV as a marker of aortic stiffness. According to the Moens-Korteweg and Bramwell-Hill equations,[6] the PWV, which is related to the square root of the elasticity modulus and to the thickness/radius ratio, rises in stiffer arteries. The PWV, determined from foot-to-foot transit time in the aorta, provides a simple, reproducible, noninvasive evaluation of regional aortic stiffness.[7,15,16] The critical factors are precise measurements of this transit time, the length of the vascular segments, and the difficulty of obtaining pulse wave recordings under certain conditions (obesity, for instance).[6] Transcutaneous determination of the vessel length is an approximation that might underestimate the vascular length, an error that is especially likely to occur in elderly patients with unfolded, tortuous aortae.[8] In the present study, 17% of the total population were over 70 years old. Repeatability studies, checks using Bland and Altman diagrams,[17] and modern computer technology[14] now make it quite

TABLE VIII. AGE- AND MAP-ADJUSTED BRACHIAL PULSE PRESSURE

	PP (MM HG)	AGE (YEARS)	MAP (MM HG)	ADJUSTED PP (MM HG)
No site	60	59	103	65
Lower limb site	72	69	106	71
Cerebrovascular site	71	68	105	71
Lower limb and cerebrovascular sites	82	75	105	78

Values are means. On the basis of the Scheffé test, pulse pressure was significantly different ($p=0.005$) between the "no site" and the three other groups. MAP=mean arterial pressure; PP=pulse pressure

feasible to simply and quickly investigate aortic stiffness in CV epidemiologic studies. Since the principal factors modulating the level of PWV are known to be age and blood pressure,[5–7] analysis involving PWV in CV studies should be adjusted for these two parameters.

The present population was composed of young and old hypertensive subjects under long-term antihypertensive drug treatment. Although a significant proportion of the patients (25%) had DVD, this proportion was probably underestimated, since invasive explorations were not systematically performed and some cases of silent myocardial ischemia or cerebrovascular disease, for example, were probably not detected. Subjects in group II had higher rates of tobacco consumption, higher levels of plasma creatinine and glucose, and a higher incidence of drug treatment for diabetes and dyslipidemia. Furthermore, brachial pulse pressure was increased in Group II, even though the mean arterial pressure was the same as that in Group I. This finding is not surprising, since high pulse pressure is an independent CV risk marker, particularly for MI.[18–21]

We found that, in our total population, the presence of DVD was significantly related to the level of PWV independently of age and blood pressure, while the other CV risk factors and drug therapy were not associated with PWV. In the past, most studies relating PWV to plasma cholesterol and/or dyslipidemia disclosed minimal or inconsistent correlations.[6,9,22,23] Such a result is not unexpected since, at the early phase of atherosclerosis, the presence of cholesterol-induced foam cells represents soft material, which tends to decrease rather than increase arterial stiffness.[24] As suggested by others,[13,25,26] the correlation between PWV and DVD points to the presence of diffuse and calcified atherosclerotic plaques in association with the development of extracellular matrix, mainly collagen tissue. Our finding that PWV was strongly related to the number of atherosclerotic sites confirms this interpretation.

The specific effect of atherosclerosis of the lower limbs and the abdominal aorta on PWV and pulse pressure may be explained on the basis of pulsatile arterial hemodynamics.[6] Whereas mean arterial pressure remains almost constant along the arterial tree, pulse pressure increases significantly from central to peripheral arteries because of a predominant increase in systolic blood pressure and a slight decrease in diastolic blood pressure. This hemodynamic pattern is the physiologic consequence of progressive stiffening and reduction in the caliber of large arteries, and also of the particular timing of reflected pressure waves inside the arterial tree. Indeed, the aortic blood pressure curve may be considered as the mathematical summation of an incident pressure wave, coming from the heart and propagated along the arterial tree, and a reflected wave, returning to the heart from reflection sites located at the origins of resistant vessels. The forward wave is influenced by the pattern of ventricular ejection and the degree of aortic stiffness. The amplitude and timing of the reflected wave depends not only on arterial stiffness, but also on the distance between the reflection sites and the heart. In CV disease-free middle-aged individuals, arterial stiffening remains modest and reflection points are principally observed at the early narrowing of small resistant vessels, causing a return of reflection waves during the diastolic component of the aortic pressure wave with a relatively low peak aortic systolic and pulse pressure. In older individuals, particularly those with hypertension, arterial stiffness increases markedly and additional reflecting sites operate closer to the heart, causing a return of reflected waves during the systolic component of the pressure wave, with the apparition of a late systolic aortic peak. In subjects with DVD of the lower limbs and the abdominal aorta, in addition to arterial stiffening, reflections sites are much closer to the heart as a consequence of calcified and stiffened atherosclerotic plaques, particularly at the origin of the renal arteries and at the site of aortic bifurcation.[6,7] In the latter case, arterial tapering also contributes to the local alterations.

The present study was somewhat limited by its own design, including a relatively small number of patients, a possible underestimation of DVD, and finally, a qualitative assessment of DVD. Nevertheless, we found consistent associations between PWV and the presence, extent, and localization of atherosclerosis. Since these subjects with significant atherosclerotic alterations, such as arterial stenosis, aortic aneurysm, or MI, were often asymptomatic, aortic PWV can be proposed in hypertensive populations as a systematic first-step measurement for risk stratification.

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