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Assessment of Vascular Aging and Atherosclerosis in Hypertensive Subjects: Second Derivative of Photoplethysmogram Versus Pulse Wave Velocity

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The pulse wave velocity (PWV) and the photoplethysmogram (PTG) are noninvasive methods for evaluating the pulse wave. The PWV has been associated with age and arterial hypertension, and an index of the second derivative of PTG (SDPTG) is correlated with age and other risk factors for atherosclerosis. The aim of this study was to compare SDPTG and PWV concerning the influencing factors of vascular compliance, including age and atherosclerosis, in a large hypertensive population. We studied consecutively 524 essential hypertensives, 140 with atherosclerotic alterations (AA), defined on the basis of clinical events including coronary heart disease, peripheral vascular disease, stroke, and abdominal aorta aneurysm. The PWV carotid-femoral was measured by a Complior device and the SDPTG was recorded by Fukuda FCP-3166. The augmentation index (AUI) of PTG was defined as the ratio of the late systolic peak to that of the early systolic peak in the pulse. The SDPTG consists of an a,b,c, and d wave in systole and an e wave in diastole; an SDPTG aging index (AI) was calculated as (b-c-d-e)/a. The patients with AA presented a higher PWV (14.9 ± 4 m/sec *v* 12.4 ± 2 m/sec, $P < .001$), PTG AUI (0.322 ± 0.16 *v* 0.252 ± 0.09, $P < .001$), and SDPTG AI (−0.093 ± 0.03 *v* −0.271 ± 0.018, $P < .001$). However, in patients 60 years of age, only PWV remained higher in those with AA, whereas in patients >60 yr, both PWV and SDPTG AI remained higher in those with AA. The PWV was independently influenced by age, systolic blood pressure, glucose, AA, and plasma creatinine, whereas the PTG AUI was influenced by age and systolic pressure and the SDPTG AI by age and AA. In a logistic regression model for the presence of AA, including age, plasma creatinine, smoking, and diastolic BP, PWV was a significant independent determinant of AA, whereas SDPTG-AI weakly entered into the model. This study provides evidence that the aortic PWV reflects better than the SDPTG the modifications of the arterial compliance related to age, blood pressure, and atherosclerosis. However, the SDPTG AI may be useful for evaluation of vascular aging in hypertensives. Am J Hypertens 2000;13:165–171

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Aortic stiffness increases with age[1] and hypertension,[2] and is also enhanced in subjects with diabetes mellitus,[1] atherosclerosis,[3] and end-stage renal disease.[4] Pulse wave analysis is a well recognized way to evaluate aortic stiffness and, consequently, could be useful to evaluate the vascular effects of aging, hypertension, and atherosclerosis. There are different noninvasive methods to assess the arterial pulse wave, such as the carotid-femoral pulse wave velocity (PWV)[4,5] and digital photoplethysmography (PTG).[6–9] The PWV is the velocity of pulse wave to travel a given distance between two sites of the arterial system and has been correlated with age and blood pressure.[4–5] The PTG has been demonstrated as a useful technique to evaluate the volume changes of peripheral vessels, reflecting both central and peripheral arterial factors.[6–8] The second derivative of PTG waveform has been described to reflect the ascending aortic systolic pressure wave and is also correlated with age and risk factors of atherosclerosis in Japanese population,[6,9] but has not yet been described in an occidental population.

The goal of the present study was: 1) to determine the factors influencing aortic stiffness estimated by carotid-femoral PWV and PTG and SDPTG, and 2) to compare the aortic PWV and the parameters of PTG and SDPTG as better markers of atherosclerotic and aging-related vascular damages in a hypertensive population that was never treated or even medically treated by antihypertensive agents.

MATERIAL AND METHODS

Study Cohort From January 1996 to January 1998, 524 patients with essential hypertension entered the department of Internal Medicine of Broussais Hospital for a CV checkup ordered by their general practitioner or their cardiologist, because of the presence of one or several CV risk factors with or without previously verified atherosclerotic alterations (AA). In never treated hypertensive subjects (n = 90), high blood pressure was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg, measured by sphygmomanometer in the supine position, with a minimum of three casual measurements during the last month. In treated hypertensive subjects (n = 434), patients were included regardless of whether blood pressure was well controlled (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg). Patients with all forms of secondary hypertension, on the basis of classical laboratory and radiology tests, with insulin-dependent diabetes or with severe renal insufficiency (creatinine >300 μmol/L) were not included in the study. The group consisted of 524 hypertensive consecutive patients (230 male, 294 female), with a mean age of 60 ± 13 years. Each subject provided informed consent for the study, which was approved by our institutional review board.

All demographic, clinical, and laboratory data from the examination were obtained at the inclusion of the protocol during hospitalization. The presence of AA in 140 patients was based in the following criteria for hypertensive patients, according to the International Classification of Diseases (ninth revision): 1) coronary heart disease (CHD), defined as a previous history of angina pectoris (precordial chest pain precipitated by exertion and relieved by rest or nitrates) confirmed by coronary angiography, myocardial infarction (MI) (based on the medical history and records or on the findings of typical sequelae of infarction on ECG), coronary artery bypass surgery, or percutaneous transluminal angioplasty; 2) cerebrovascular disease, defined as a history of transient ischemic attacks, or thrombotic stroke verified by computed tomography without evidence of embolic cardiopathy; or severe carotid-artery stenosis (>70%) verified by Doppler echography or angiography, or surgically treated; 3) peripheral vascular disease, defined as typical symptoms of lower limb vascular disease or disease of major arteries including splanchnic circulation, or surgery or percutaneous transluminal angioplasty for this disorder; and 4) abdominal aortic aneurysm assessed by Doppler echography or computed tomography, or surgery for this disorder.

A total of 140 patients had presented with AA involving at least one vascular site, including coronary heart disease (84 patients), peripheral vascular disease (42 patients), cerebrovascular disease (31 patients), and abdominal aorta aneurysm (31 patients). The mean number of vascular sites involved by AA in the population of the 140 patients was 1.43 ± 0.65 per patient.

Methods The measurements were performed in the morning after an overnight fast with each patient in supine position. Brachial blood pressure (BP) was measured using a mercury sphygmomanometer after 15 min of rest. The mean BP (MBP) was calculated as MBP = DBP + (SBP − DBP)/3. Five measurements 2 min apart were averaged. Venous samples for biochemistry analysis were collected after an overnight fast. Left ventricular hypertrophy on ECG was defined as a Sokolow index >35 mm.

After blood pressure determination, the PWV, PTG, and SDPTG measurements were performed in a controlled environment at 22° ± 2°C. The PWV was determined using an automatic device, Complior (Colson, Garges les Gonesses, France), which allowed an on-line pulse wave recording and automatic calculation of PWV.[5] Briefly, common carotid artery and femoral artery pressure waveforms were recorded noninvasively using a TY-306-Fukuda pressure-sensi-

tive 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.[10] 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 ≥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), whereas pulse transit time (t) was automatically determined by the Complior; PWV was automatically calculated as PWV = D/t. The validation of this automatic method and its reproducibility have been previously described, with an intraobserver repeatability coefficient of 0.935 and an interobserver reproducibility coefficient of 0.890.[5]

The PTG and SDPTG were performed by a Fukuda FCP-3166, as had already been described.[6,9] Briefly, the device is a photoplethysmogram, equipped with double differentiation circuits, with the sensor positioned at the cuticle of the second digit of the left hand. The PTG measures changing absorption of light by hemoglobin, which reflects changes in blood flow volume. The FCP-3166 contained automatic analysis of each SDPTG wave, and total frequency response was adjusted to 10 Hz. A schema of the curves obtained in PTG and SDPTG are shown in Figure 1. The augmentation index of PTG (AUGI) was defined as PT2-PT1/MA, where PT2 = the height of the second component of PTG, PT1 = the height of the first component of PTG, and MA = maximum amplitude of PTG. The SDPTG consists of four waves in systole (a,b,c, and d, respectively, or first, second, third, and fourth components) and one in diastole (e). We measured the height of each wave from the baseline, with the values above the baseline being positive and those under it negative. The d/a ratio, defined as the ratio of the height of d-wave to that of the a-wave (%), was calculated automatically. The aging index (AGI), defined as (b-c-d-e)/a according to Takazawa et al,[9] was calculated manually. The intraobserver repeatability of measurements according to Bland and Altman[10] was 8%.

Statistical Analysis Data were expressed as mean ± SD. The Student *t* test was used for comparison of normally distributed continuous variables. Differences in frequency were tested by χ^2 analysis. Statistical analysis was performed on the NCSS 6.0.21 software.[11] A *P* value <.05 was considered significant. All testing was two-sided. Multiple regression analysis was performed to assess linear associations between aortic pulse wave velocity, SDPTG and PTG indexes, and determinants of clinical, biochemical, and cardiovascular parameters. Logistic regression analysis was used to assess the correlation between the presence of AA (1 = yes, 0 = no) and determinants of clinical, biochemical and cardiovascular parameters.

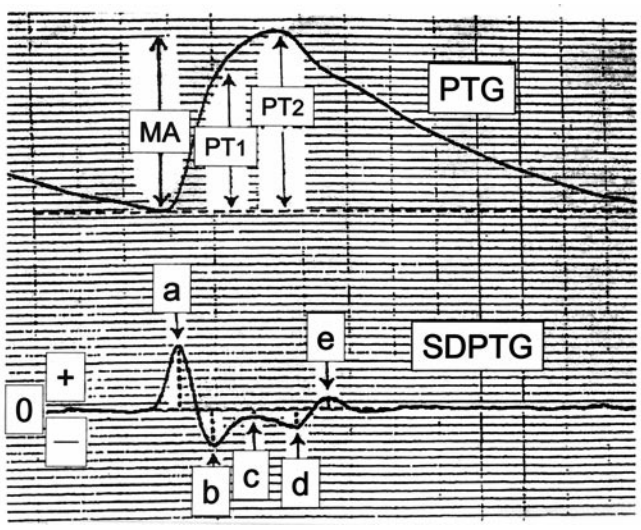

FIGURE 1. *Measurements of the indexes from PTG and SDPTG: The augmentation index of PTG was defined as PT2-PT1/MA, where PT2 = the height of the late systolic component (m V/V), PT1 = the height of the early systolic component, and MA = maximum amplitude of PTG. The SDPTG consists of four waves in systole (a,b,c,d, respectively, = first, second, third, and fourth components) and one in diastole (e). The height of each wave was measured from the baseline, with the values above the baseline being positive and those under it negative. The d/a ratio was defined as the ratio of the height of d-wave to that of the a-wave (%) and the aging index defined as (b − c − d − e)/a, was calculated manually.*

RESULTS

Table 1 shows the characteristics of the patients according to the presence or absence of AA. Patients with AA were older ($P < .0001$), with a higher proportion of men ($P = .001$). Although mean BP was not significantly different in the two groups, diastolic BP was lower ($P = .0002$), and systolic and pulse pressures were higher in the group of patients with AA ($P = .001$ and $P < .0001$, respectively). There was a higher proportion of current smokers ($P < .0001$) in the group of patients with AA that presented a higher tobacco lifelong dose ($P < .0001$). Furthermore, the patients with AA exhibited a higher duration of antihypertensive treatment ($P < .0001$) and a higher plasma creatinine ($P < .0001$), while showing a lower BMI ($P = .03$) and a lower heart rate ($P = .03$) when compared to the patients without AA. Plasma glucose, total/HDL cholesterol ratio, and

TABLE 1. CHARACTERISTICS OF PATIENTS ACCORDING TO THE PRESENCE OR ABSENCE OF ATHEROSCLEROTIC ALTERATIONS

Parameter	Atherosclerotic Alterations (n = 140)	No Atherosclerotic Alterations (n = 386)	*P* Value
Clinical parameters			
Age (years)	67 ± 10	57 ± 6	< .0001
Sex (M/F)		134/190	.001
Body mass index (kg/m^2)	25.7 ± 4	27 ± 4	.03
Current smoker (ratio)	0.30 ± 0.5	0.15 ± 0.4	< .0001
Tobacco lifelong dose (pack-years)	20 ± 14	8 ± 8	< .0001
Duration of antihypertensive therapy (years)	13 ± 9	9 ± 9	< .0001
ECG left ventricular hypertrophy (ratio)	0.1 ± 0.2	0.1 ± 0.1	—
Plasma glucose (mmol)	6.33 ± 0.1	6.07 ± 0.08	—
Total/HDL cholesterol (ratio)	4.34 ± 1.6	4.2 ± 1.4	—
Plasma creatinine (μmol/L)	104.7 ± 20	86.9 ± 12	<.0001
Hemodynamic parameters			
Systolic BP (mm Hg)	149 ± 17	143 ± 10	.001
Diastolic BP (mm Hg)	79 ± 9	83 ± 12	.0002
Mean BP (mm Hg)	102 ± 13	103 ± 13	—
Pulse pressure (mm Hg)	71 ± 14	60 ± 8	< .0001
Heart rate (beats/min)	67 ± 10	69 ± 10	.03
Pulse wave velocity (m/sec)	14.9 ± 4	12.4 ± 2.6	< .0001
PTG Augmentation index	0.322 ± 0.16	0.252 ± 0.09	< .0001
SDPTG D/a ratio	−0.235 ± 2	−0.19 ± 1	—
SDPTG Aging index	−0.093 ± 0.03	−0.271 ± 0.018	< .0001

Continuous variables are expressed as means ± SD.

See text for abbreviations.

prevalence of left ventricular hypertrophy were not significantly different.

Mean PWV was 14.9 ± 4.0 m/sec in the group of patients with AA, and 12.4 ± 2.6 m/sec for the patients without AA ($P < .0001$). Also, the PTG AUGI (0.322 ± 0.16 *v* 0.252 ± 0.09) and SDPTG AGI (−0.093 ± 0.03 *v* −0.271 ± 0.018) were higher in the patients with AA compared to those without AA. The d/a ratio was not significantly different in the two groups of patients.

Table 2 shows the values of the PWV, PTG, and SDPTG indexes according to the presence of AA in two different ranges of age (<60 years or >60 years). We noted that, in patients <60 yr, only the PWV was significantly higher in patients with AA (13.1 ± 0.5 m/sec) compared to patients without AA (11.5 ± 0.2 m/sec) ($P < .01$). However, in those patients >60 yr, the PWV and the SDPTG AGI were significantly higher in patients with AA. We also observed that the values of PWV of younger patients with AA were not different from those of patients >60 yr without AA.

Age ($P < .0001$), systolic blood pressure ($P < 0.0001$), plasma glucose ($P = .004$), presence of AA ($P = .0005$), and plasma creatinine ($P = .003$) were

TABLE 2. PULSE PRESSURE, PULSE WAVE VELOCITY, AND INDICES OF PTG AND SDPTG ACCORDING TO AGE AND THE PRESENCE OF ATHEROSCLEROTIC ALTERATIONS

	Age <60 Years (n = 248)		Age >60 Years (n = 276)	
Parameter	No AA (n = 215)	AA (n = 33)	No AA (n = 168)	AA (n = 107)
Pulse pressure (mm Hg)	55 ± 1	60 ± 2.8	66 ± 1.2	74 ± 1.5
Pulse wave velocity (m/sec)	11.5 ± 0.2	13.1 ± 0.5*	13.7 ± 0.2	15.6 ± 0.3*#
PTG Augmentatiom index	0.21 ± 0.01	0.25 ± 0.03	0.29 ± 0.01	0.34 ± 0.01
SDPTG Aging index	−0.37 ± 0.02	−0.26 ± 0.06	−0.13 ± 0.02	−0.04 ± 0.03*

AA, atherosclerotic alterations.

* $P < .01$, no AA versus AA in each age range, by two-factor analysis of variance.

TABLE 3. MULTIPLE REGRESSION ANALYSIS OF PULSE WAVE VELOCITY

Parameter	Regression Coefficient	Standard Error	T Value	*P* Value
Pulse wave velocity (m/sec)				
Age (years)	0.0088	0.0094	9.37	< .0001
Systolic blood pressure (mm Hg)	0.039	0.0057	6.8	< .0001
Plasma glucose (mmol/L)	0.194	0.068	2.8	.004
Atherosclerotic alterations (yes or no)	1.003	0.290	3.45	.0005
Plasma creatinine (μmol/L)	0.015	0.0053	2.95	.003
SDPTG Aging index				
Age (years)	0.0092	0.0011	7.81	< .0001
Atherosclerotic alterations (yes or no)	0.085	0.036	2.33	.019
PTG augmentation index				
Age (years)	0.0035	0.0006	5.49	< .0001
Systolic blood pressure (mm Hg)	0.0013	0.004	3.29	.001

(Model R^2 = 0.362; F ratio = 48.79; model probability < .0001), acceleration index (model R^2 = 0.157; F ratio = 16.10; model probability < .0001), aging index (model R^2 = 0.180; F ratio = 15.46; model probability < .0001) and augmentation index (model R^2 = 0.180; F ratio = 15.46; model probability < .0001).

the only independent factors modulating PWV (Table 3). Sex, lipids, smoking, duration of antihypertensive therapy, and presence of any antihypertensive drug did not significantly take part in the multiple regression analysis (data not shown). Nevertheless, only age ($P < .0001$) and the presence of AA ($P < .05$) were independent factors modulating SDPTG AGI, whereas age and systolic blood pressure were the only significant factors modulating PTG AUGI (Table 3).

For the analysis of the independent factors modulating the presence of atherosclerotic alterations, we constructed one model of logistic regression analysis including age, plasma creatinine, tobacco lifelong dose, PWV, AGI, and diastolic blood pressure (Table 4). In this model, plasma creatinine ($P < .001$), tobacco lifelong dose ($P < .001$), age ($P = .001$), and PWV ($P = .02$) were significant independent modulating factors, whereas AGI ($P = .06$) and diastolic blood pressure ($P = .08$) were not significant.

TABLE 4. LOGISTIC REGRESSION ANALYSIS OF ATHEROSCLEROTIC ALTERATIONS

Parameter	Regression Coefficient	χ^2	*P* Value
Atherosclerotic alterations (yes, no)			
Model R-squared = 0.211;			
model χ^2 = 112.87;			
model probability < 0.0001.			
Tobacco lifelong dose (pack/years)	0.026	14.71	.0001
Plasma creatinine (μmol/L)	0.018	14.34	.0001
Age (years)	0.043	10.71	.001
Pulse wave velocity (m/sec)	0.096	5.03	.02
Aging Index	0.816	3.61	.06
Diastolic blood pressure (mm Hg)	−0.02	3.04	.08

DISCUSSION

The salient findings of this study were that, in a population of treated or untreated subjects with essential hypertension, aortic PWV was strongly related to age, blood pressure, and atherosclerosis, whereas the parameters of PTG or SDPTG were only strongly related to age. Thus, the PWV seems to be a better marker of the presence of atherosclerosis, both in young and elderly patients, than the SDPTG AGI, which is related to AA only in older patients.

In the present study, we used PWV, PTG, and SDPTG to evaluate the aortic stiffness and elasticity. According to the Moens-Korteweg and Bramwell-Hill equations,[4] the PWV is related to the square root of the elastic modulus and to the thickness/radius ratio. Thus, PWV increases in stiffer arteries, which can explain the increased PWV found in our hypertensive patients with atherosclerotic alterations. The PWV determined from foot-to-foot transit time in the aorta, as performed in our study, offers a simple, reproducible and noninvasive evaluation of regional aortic stiffness.[12,13] Indeed, in our study, it was possible to perform PWV measurements in a large population of hypertensive patients, providing accurate information concerning modifications in the arterial stiffness related to age or atherosclerosis. Moreover, the indices of PTG and SDPTG also provided valuable information concerning vascular modifications of aging but not of atherosclerosis.

These distinctive features could be explained by specific differences between the two techniques. The PWV reflects arterial stiffness based on the analysis of two arterial curves detected at the same time in large arteries, and gives results that are independent of wave reflection.[5] On the other hand, the features of the

photoplethysmograph are caused by wave reflection, as this technique evaluates the volume changes of peripheral vessels,[6] Thus, factors that alter wave reflection such as heart failure, differences in heart rate, and drug treatment, would be expected to have a greater effect on the PTG and SDPTG than on PWV. In our study, no patients with heart failure were included, and the heart rate and drug treatment seemed not to interfere with the features of PTG. Therefore, the PWV seems to be a more accurate method than PTG to evaluate aortic compliance and stiffness. In our study, in which, for the first time, two noninvasive methods for aortic distensibility were compared in a large cohort population of hypertensive patients, the PWV was better correlated with the factors that usually induce modifications in the aortic stiffness than were PTG and SDPTG. Apart from the principal factors known to modulate the level of PWV, such as age and blood pressure,[3,4,14] our study showed that the presence of atherosclerosis also modulates, independently, the PWV. Moreover, as observed in PWV, the indices of SDPTG could be changed in consequence of the modifications of the waveforms produced by age or atherosclerosis, as suggested by Takazawa.[9] In this study, in a Japanese population, the Aging Index was higher not only in older subjects (as we have demonstrated in our study), but also in patients presenting risk factors for atherosclerosis. Nevertheless, in our study, the Aging Index of SDPTG was significantly associated with atherosclerosis only in older persons, whereas, in the overall population, the association was not strong.

As suggested by others,[14,15] the present correlation between PWV and AA points to the presence of diffuse and calcified atherosclerotic plaques in association with the development of extracellular matrix, mainly collagen tissue. This hypothesis may be reinforced by the fact that younger patients with atherosclerosis showed values of PWV similar to those of older patients without AA, that is, an "accelerated vascular aging." Previous studies have tried to correlate PWV with dyslipidaemia or cholesterol level, but minimal or inconsistent correlations were found.[15] This lack of association is not unexpected, as the presence of cholesterol-induced foam cells tends to decrease, rather than increase, arterial stiffness.[16] Moreover, these studies were performed in normotensive subjects, and the presence of atherosclerosis was not clinically evaluated. In our study, the presence of atherosclerosis was based on accurate clinical criteria and was confirmed in only a few patients. However, these clinical criteria seem to be more appropriate than simple correlation with cholesterol levels, which does not imply a direct correlation with atherosclerotic plaques.

There are some limitations concerning these two different methods of evaluation of aortic stiffness that could interfere with the results. First, the difference in repeatability of SDPTG and PWV could influence the different results obtained with each method. Although expressed differently, the repeatability for both is $<8\%$, suggesting that variability does not interfere consistently in the observed results. Second, the length of the vascular segments could be overestimated by the PWV method, but the correlation coefficient of the relationship between PWV and time delay is 0.96.[5] In addition, transcutaneous determination of the vessel length is an approximation that might underestimate the vascular length, an error that might arise especially in elderly patients with unfolded tortuous aorta. Furthermore, the SDPTG remains unknown in occidental populations. The correlation between SDPTG and ascending aortic pressure was well established only in Japanese populations,[6,9] and this correlation could be different in other populations. Our study is the first to demonstrate the value of SDPTG in a large occidental population. Anyway, the PTG basically shows a peripheral volume pulse and not a pressure pulse, and therefore can suffer the effects of venous pulsation on the PTG wave. The quantification of this effect has not yet been quantified but, as the augmentation index of PTG is well correlated with the ascending aortic augmentation index,[6] the effect seems to be irrelevant. Based on these remarks, a comparison between the SDPTG and PWV could appear to be inappropriate. However, the possibility of performing both methods in a large hypertensive population seemed to us to be relevant and important to assess, noninvasively, the arterial system.

In conclusion, the present study has shown, in a cohort of untreated and treated hypertensive subjects, that aortic PWV was a better marker of the presence of AA than were SDPTG or PTG indices. Both PWV and SDPTG may be useful for evaluation of vascular aging. However, PWV seems to be useful for screening of arteriosclerotic independently of age, whereas SDPTG would be useful in this regard only in the elderly.

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