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Distension Capacity of the Carotid Artery and Ambulatory Blood Pressure Monitoring

Effects of Age and Hypertension

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In hypertension, the principal components of the mechanical stress acting on the arterial wall may be evaluated not only from the level of peak systolic and end-diastolic blood pressure but also by the level of pulse pressure and variability of blood pressure measured by ambulatory monitoring. The purpose of the present study was, in a population of 51 subjects with essential hypertension, to determine the influence of these parameters and of heart rate on the distension capacity of the common carotid artery, measured noninvasively by high-resolution echo-tracking techniques. The pulsatile change in diameter of the carotid artery diameter, estimated either in absolute or relative values, was shown to be significantly and independently correlated with four mechanical parameters deduced from daytime ambulatory blood pressure measurements: baseline diastolic blood pressure (the lower the diastolic blood pressure, the higher the distension capacity; r = −0.44; $P < .001$); pulse pressure (the higher the pulse pressure, the higher the distension capacity; r = 0.32; $P < .024$); variability of diastolic blood pressure (the higher the variability, the higher the distension capacity; r = 0.37; $P < .008$); and mean heart rate (the higher the heart rate, the more reduced the distension capacity; r = −0.28; $P < .05$). Multiple regression analysis indicated that mean diastolic blood pressure and its variability, mean heart rate, and pulse pressure acted independently on carotid artery distension, even after adjustment for age. The present study suggests for the first time that, in humans, hypertension may act on the arterial wall not only through the amplitude of peak systolic and end-diastolic blood pressure but also through several other mechanical factors involving the level of pulse pressure and heart rate and also blood pressure variability. Thus, in addition to the level of blood pressure, carotid artery distension is specifically influenced by two factors independently implicated in the epidemiologic cardiovascular risk: pulse pressure and heart rate. Am J Hypertens 1995;8:343–352

KEY WORDS: **Hypertension, arterial distensibility, echo tracking techniques, ambulatory blood pressure.**

Hypertension, one of the major risk factors of cardiovascular disease, is usually diagnosed on the basis of two specific points of the blood pressure curve: peak systolic blood pressure and end-diastolic blood pressure. These two points give a very approximate view of the cyclic characteristics of the blood pressure curve. Indeed, through these two points, it is possible to draw only one straight line, but it is also possible, in contrast, to represent an infinite number of pulsatile blood pressure curves. If hypertension is considered as a mechanical factor acting on the arterial wall, thus causing an increased cardiovascular morbidity and mortality in the human population, it is not only the

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level of systolic and diastolic blood pressure that we should evaluate, but rather the totality of the characteristics of the blood pressure curve. Epidemiologic studies have shown that, in patients over 50 years of age, systolic is a stronger cardiovascular risk factor than diastolic blood pressure.[1] In addition, pulse pressure[2,3] and heart rate[4,5] have been reported to be independent cardiovascular risk factors, particularly for cardiac morbidity and mortality. Finally, increased variability of blood pressure has been shown to contribute to target organ damage in human populations.[6,7] Taken together, such findings indicate that several mechanical particularities of the blood pressure curve, such as peak systolic, end-diastolic, and mean arterial pressure, and also heart rate, pulse pressure, and variability of blood pressure, should be taken into account in the evaluation of cardiovascular risk. In this view, ambulatory blood pressure should be considered as a reference method for this kind of investigation.

Usually, the target organ damage evaluated in the hypertensive population is described in terms of cardiovascular morbid events, such as heart attacks, congestive heart failure, or strokes. More recently, intermediate criteria, such as the degree of cardiac hypertrophy or the frequency of rhythmic disorders, have been widely used.[8,9] However, large arteries, through rupture or thrombosis, are the principal sites of the complications of hypertensive vascular disease. Thus, it is important in hypertension to relate the characteristics of the blood pressure curve to the mechanical properties of the arteries. Since pulse pressure is an independent factor of cardiovascular risk[2,3] and since pulse pressure acts principally on the distension capacity of the arteries,[10] it should be relevant to evaluate the influence of this pressure-induced mechanical signal on the distension capacity of the arterial wall. Recent innovations in echo-tracking techniques of high resolution permit a safe, noninvasive evaluation of the distension capacity of the carotid artery with an elevated degree of reproducibility.[11–13]

The purpose of the present study was to determine, in a population of hypertensive subjects, the distension capacity of the carotid artery as a function of several mechanical signals deduced from ambulatory blood pressure measurements, ie, systolic, diastolic, and mean arterial pressure, but also pulse pressure and variability of blood pressure. The relationship between heart rate and arterial distension capacity was also investigated.

MATERIALS AND METHODS

Patients Fifty-one subjects (32 men and 19 women) with mild to moderate hypertension were selected during 1990 to 1991 from the Hypertensive Clinic of Broussais Hospital, Paris. Based on the auscultatory method described below, diastolic blood pressure determined in consultation was between 90 and 105 in all subjects with sustained moderate hypertension. The age range was between 21 and 78 years; mean age was 46 ± 13 years (±1 SD). Mean weight and height were, respectively, 70 ± 13 kg and 169 ± 8 cm. On the basis of standard clinical and biologic investigations,[14] all subjects were considered to have uncomplicated essential hypertension. Antihypertensive therapy had been stopped at least 4 weeks previously. No subject had coronary ischemic heart disease, congestive heart failure, or any renal or cerebral complication. Informed consent, based on a detailed description of the procedure, had been obtained from all patients.

For the investigation, a blood sample was taken after overnight fasting, at 8 AM, for plasma glucose and lipid determinations according to standard techniques. Casual blood pressure was measured in the supine position after 10 min rest. Patients then underwent carotid artery measurements and blood pressure monitoring according to the methodology described below.

Casual Blood Pressure Measurements Casual blood pressure was measured after 10 min rest in the supine position using a mercury sphygmomanometer. An average of three measurements was taken for each patient. The Korotkoff noise phase I was used for the determination of systolic blood pressure; phase V was used for the evaluation of diastolic blood pressure. Mean blood pressure was calculated as the sum of diastolic blood pressure plus one-third of the pulse pressure, and pulse pressure as the difference between systolic and diastolic blood pressure.

Ambulatory Blood Pressure Monitoring Automated blood pressure monitoring was carried out in each patient using a Novacor apparatus (model Diasys 200 R, Rueil-Malmaison, France) to measure and record blood pressure and heart rate over a full 24-h period. The reliability of this method has been published in detail elsewhere.[15,16] Recordings were performed every 15 min during the 24 h. Ambulatory monitoring was undertaken for a full active day; the patient worked as usual during the day and then went home as usual in the evening. As previously published,[17] recordings that showed a calculated pulse pressure >100 mm Hg or <20 mm Hg with a systolic blood pressure >100 mm Hg were deleted before further data analysis. Each full day's recording was divided into an activity (diurnal) period (7 AM to 10 PM) and a nonactivity (nocturnal) period (10 PM to 7 AM). Based on the patients' diaries, this classification corresponded well to waking and sleeping times.

Mean values were used for statistical analysis and variability was assessed on the basis of the absolute standard deviation (SD) evaluated in each subject.

On the basis of the mean value of diurnal diastolic blood pressure (DBP) measurements, subjects were classified into two groups according to their diastolic blood pressure (DBP < 85 or ≥ 85 mm Hg). Subjects with DBP < 85 mm Hg fulfill the classical criteria of "white-coat hypertension."[6,7,15–17] In addition, to evaluate the role of age on hemodynamic parameters, the subjects of the same population were classified as younger (<45 years) or older (≥45 years). The clinical characteristics of these subgroups are indicated in Table 1. Older subjects had a slightly higher level of plasma glucose and cholesterol ($P < .05$).

Carotid Artery Parameters The vessel wall motion of the common carotid artery was measured by using an original pulsed ultrasound echo-tracking system based on the Doppler shift.[11] The operating frequency of the device was 7.5 MHz. Details of this method have been described elsewhere.[11,14] Briefly, this system enables the transcutaneous assessment of the displacement of the arterial wall during the cardiac cycle and, hence, the time-dependent changes in arterial diameter relative to its initial diameter at the start of the cardiac cycle. The availability of the electrocardiogram (ECG) trigger facilitates the detection of the peak distension of the artery relative to its initial diameter. A typical displacement waveform or the anterior and posterior walls of the common carotid artery permits recording of the successive values of peak systolic (Ds) and end-diastolic (Dd) diameters, the stroke change in diameter during systole (Ds − Dd), and the relative stroke change in diameter [(Ds − Dd)/Dd], which were computed from the recording. The distension capacity of the carotid artery is thus evaluated either in absolute (Ds − Dd) or in relative [(Ds − Dd)/Dd] values. Using this procedure, it was previously shown that the side (right or left) of measurement did not influence the values of the arterial dimensional data.[14]

The repeatability of the carotid artery measurements was previously studied in five normotensive subjects.[14] The coefficient of variation (standard deviation expressed as a percentage of the mean of several successive measurements) was used for this purpose. First, repeatability was assessed during the recording of three to eight successive cardiac cycles. The mean coefficients of variation determined under these conditions were, respectively, 1%, 6%, and 6% for Dd, Ds − Dd, and (Ds − Dd)/Dd. Second, repeatability was assessed during 12 measurements performed by each of two observers over a 90-min period in five subjects. Each of the 12 measurements was the mean of three to eight values corresponding to three to eight cardiac cycles. Under these conditions, the mean intraobserver coefficient of variation was 3%, 8% and 10%, for Dd, Ds − Dd, and [(Ds − Dd)/Dd], respectively. In the present study, all measurements were performed by the same observer (RA).

Statistical Analysis Statistical analysis[18] was performed with SYSTAT for Windows version 5 statistical software (Evaston, IL). Values are expressed as means ± SD. Comparison of the mean values between two populations was performed using the unpaired Student t Test. Simple and stepwise multiple regression analyses were performed according to standard techniques.[18] The significance level was fixed at .05.

TABLE 1. CLINICAL LABORATORY AND BLOOD PRESSURE VALUES IN SUBJECTS ACCORDING TO THEIR DIURNAL DIASTOLIC BLOOD PRESSURE AND AGE

	DBP < 85 mm Hg (n = 25)	DBP ≥ 85 mm Hg (n = 26)	Age < 45 years (n = 25)	Age ≥ 45 years (n = 26)
Age (years)	43 ± 15	49 ± 10	36 ± 6	56 ± 8
Sex (M:F)	18:7	14:12	16:9	16:10
Weight (kg)	67 ± 11	72 ± 13	69 ± 10	71 ± 14
Height (cm)	169 ± 9	169 ± 7	169 ± 8	168 ± 9
Total cholesterol (mmol/L)	5.7 ± 1	6 ± 1.2	5.5 ± 0.9	6.2 ± 1.1*
Serum glucose (mmol/L)	5.5 ± 0.5	5.5 ± 0.5	5.3 ± 0.5	5.7 ± 0.6*
Sokolow index (mm)	25 ± 9	24 ± 7	24 ± 8	25 ± 8.6
Serum creatinine (mmol/L)	87 ± 24	89 ± 19	81 ± 14	94 ± 25
Serum potassium (mmol/L)	4.3 ± 0.3	4.1 ± 0.4	4.2 ± 0.4	4.2 ± 0.3
Serum triglycerides (mmol/L)	1.0 ± 0.4	1.4 ± 0.7	1.2 ± 0.6	1.3 ± 0.6
Auscultatory SBP (mm Hg)	147 ± 15	155 ± 21	146 ± 17	154 ± 20
Auscultatory DBP (mm Hg)	92 ± 10	98 ± 10	93 ± 13	97 ± 7

*$P < .05$, *age > 45 v age < 45 years.*

All values except male:female ratio are mean ± SD.

RESULTS

Mean Values Table 2 shows that, whereas blood pressure and its variability were identical when the subjects were divided into those who were younger or older, the classification into subjects with DBP < 85 or DBP ≥ 85 mm Hg on the basis of blood pressure monitoring indicates that subjects with DBP ≥ 85 mm Hg had a higher systolic (P = NS), diastolic ($P < .001$), and mean ($P < .001$) arterial pressure but a slightly lower pulse pressure ($P < .04$). No significant correlation was observed between mean arterial pressure and pulse pressures. The changes predominated during the day. For all parameters presented in Table 2, variability was identical whether subjects were classified according to age or to the level of blood pressure.

Table 3 shows that the systolic and diastolic arterial diameters are significantly larger both in subjects with DBP ≥ 85 mm Hg and in older subjects. The level of significance is more pronounced when younger and older subjects are compared ($P = .005$; $P = .015$) than when subjects with DBP < 85 and subjects with DBP ≥ 85 mm Hg are compared ($P = .042$; $P = .088$). Subsequently, subjects with higher DBP and older subjects have a significantly decreased capacity of distension, either expressed in absolute (Ds − Dd) ($P = .003$ for subjects with DBP ≥ 85 mm Hg and $P < .001$ for older subjects) or in relative [(Ds − Dd)/Dd] ($P < .0001$ for subjects with DBP ≥ 85 mm Hg and $P < .001$ for older subjects) values.

Study of Simple Correlation Coefficients Table 4

TABLE 2. AMBULATORY BLOOD PRESSURE AND HEART RATE MEASUREMENTS IN SUBJECTS WITH DBP < OR ≥ 85 mm Hg AND IN SUBJECTS YOUNGER AND OLDER THAN 45 YEARS

	DBP < 85 mm Hg (n = 25)	DBP ≥ 85 mm Hg (n = 26)	Age < 45 years (n = 25)	Age ≥ 45 years (n = 26)
24-h				
SBP (mm Hg)	126 ± 14	135 ± 18	128 ± 16	133 ± 17
SD (mm Hg)	17 ± 5	17 ± 3	17 ± 4	17 ± 4
DBP (mm Hg)	74 ± 6	91 ± 9*	81 ± 10	85 ± 13
SD (mm Hg)	14 ± 5	14 ± 3	14 ± 5	14 ± 5
MAP (mm Hg)	91 ± 6	106 ± 11*	96 ± 12	101 ± 11
SD (mm Hg)	12 ± 3	13 ± 2	13 ± 3	13 ± 3
PP (mm Hg)	52 ± 15	44 ± 13‡	47 ± 15	48 ± 15
SD (mm Hg)	14 ± 5	12 ± 3	13 ± 5	14 ± 5
HR (bpm)	77 ± 12	79 ± 9	78 ± 9	79 ± 13
SD (bpm)	15 ± 3	13 ± 4	15 ± 4	12 ± 3
Day				
SBP (mm Hg)	133 ± 14	146 ± 19	136 ± 17	139 ± 18
SD (mm Hg)	13 ± 4	13 ± 3	13 ± 3	14 ± 4
DBP (mm Hg)	78 ± 6	96 ± 9‡	85 ± 13	89 ± 11
SD (mm Hg)	12 ± 3	11 ± 2	12 ± 3	12 ± 3
MAP (mm Hg)	96 ± 6	111 ± 11*	102 ± 12	105 ± 11
SD (mm Hg)	10 ± 2	10 ± 2	10 ± 2	10 ± 2
PP (mm Hg)	55 ± 16	46 ± 14‡	51 ± 16	50 ± 16
SD (mm Hg)	14 ± 5	13 ± 3	13 ± 4	14 ± 5
HR (bpm)	83 ± 11	83 ± 10	84 ± 9	83 ± 13
SD (bpm)	13 ± 3	11 ± 4	13 ± 4	11 ± 3
Night				
SBP (mm Hg)	116 ± 14	125 ± 19	117 ± 16	124 ± 17
SD (mm Hg)	14 ± 6	14 ± 4	13 ± 5	14 ± 5
DBP (mm Hg)	68 ± 8	83 ± 10*	74 ± 12	78 ± 11
SD (mm Hg)	12 ± 6	11 ± 3	11 ± 4	12 ± 3
MAP (mm Hg)	84 ± 8	97 ± 12*	88 ± 12	93 ± 11
SD (mm Hg)	10 ± 3	11 ± 2	10 ± 3	10 ± 3
PP (mm Hg)	47 ± 14	42 ± 14‡	43 ± 14	46 ± 14
SD (mm Hg)	12 ± 5	10 ± 3	11 ± 5	11 ± 4
HR (bpm)	68 ± 13	73 ± 9	70 ± 11	72 ± 13
SD (bpm)	10 ± 5	10 ± 4	12 ± 4	12 ± 2

DBP, diastolic blood pressure; SBP, systolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; HR, heart rate; SD, variability.

**P < .001; †P < .01, ‡P < .05; DBP ≥ 85 v DBP < 85 mm Hg.*

All values are mean ± standard deviation.

TABLE 3. CAROTID ARTERY PARAMETERS IN SUBJECTS WITH DBP < OR ≥85 MM HG AND IN SUBJECTS YOUNGER AND OLDER THAN 45 YEARS

Parameter	DBP < 85 mm Hg (n = 25)	DBP ≥ 85 mm Hg (n = 26)	Age < 45 years (n = 25)	Age ≥ 45 years (n = 26)
[(Ds − Dd)/Dd)] (%)	7.0 ± 2.2	4.8 ± 1.8*	7.3 ± 2	4.5 ± 1.7§
(Ds − Dd) (μm)	470 ± 146	355 ± 115†	482 ± 142	343 ± 100§
Diastolic diameter (mm)	6.8 ± 1	7.5 ± 1.3‡	6.7 ± 0.9	7.6 ± 1.3§§
Systolic diameter (mm)	7.3 ± 0.9	7.9 ± 1.3	7.2 ± 1.0	8.0 ± 1.2§

(Ds − Dd), stroke change in carotid diameter during systole; [(Ds − Dd)/Dd)], relative stroke change in diameter, ± standard deviation.

**P < .001; †P < .01; ‡P < .05; DBP ≥ 85 mm Hg v DBP < 85 mm Hg.*

§P < .001; §§P < .01; §§§P <.05; older v younger than 45 years old.

summarizes, in subjects with DBP < 85 mm Hg, in subjects with DBP ≥ 85 mm Hg, and in the totality of the population, the simple correlation coefficients of age and blood pressure with the capacity of distension expressed as [(Ds − Dd)/Dd] or (Ds − Dd). For this analysis, only the correlation of (Ds − Dd)/Dd with diurnal blood pressure is noted in the results. The main results of the correlation study are a negative correlation between age and [(Ds − Dd)/Dd] ($r = -0.60$; $P = .001$), a negative correlation between [(Ds − Dd)/Dd] and baseline diastolic pressure ($r = -0.44$; $P = .001$) (Figure 1), and a positive correlation between [(Ds − Dd)/Dd] and pulse pressure ($r = 0.32$; $P < .02$), but the higher levels of correlation coefficients were observed in subjects with DBP < 85 mm Hg ($r = 0.47$; $P = .02$) and younger subjects ($r = 0.47$; $P < .05$).

Similar results were observed using (Ds − Dd) instead of [(Ds − Dd)/Dd] (Figure 3). In addition, [(Ds − Dd)/Dd] and (Ds − Dd) were positively related with the variability of diurnal diastolic blood pressure but not with the diurnal variability of the heart rate (Table 4 and Figure 3). (Ds − Dd) was negatively correlated with average heart rate ($r = -0.28$; $P = .054$), particularly in subjects with DBP ≥ 85 mm Hg ($r = -0.45$; $P < .05$). (Ds − Dd) was also positively related with the variability of the heart rate when measured during 24 h ($r = 0.37$, $P < .007$). None of these correlations were significant when blood pressure measured by the auscultatory method was used, instead of that seen using blood pressure monitoring.

Multiple Regression Analysis Table 5 shows that [(Ds − Dd)/Dd] was independently associated (F ratio:16.26) with age ($P < .0001$), baseline diastolic blood pressure ($P < .003$), pulse pressure ($P = .037$), and heart rate ($P < .005$). Factors influencing (Ds − Dd) were different, involving (F ratio:12.30) age ($P < .001$), pulse pressure ($P < .009$), heart rate ($P < .001$), and the variability of diastolic blood pressure ($P < .007$).

DISCUSSION

One of the principal factors acting on the vascular wall is the aging process. Hypertension is often considered to be an accelerating factor contributing to worsening the age-induced changes in arteries.[2,3,10,14] In humans it is difficult to evaluate wheth-

TABLE 4. SIMPLE CORRELATION COEFFICIENTS BETWEEN CAROTID PARAMETERS AND DIURNAL AMBULATORY BLOOD PRESSURE AND HEART RATE PARAMETERS

	Ds − Dd/Dd (%)			Ds − Dd (μm)		
	All Subjects	DBP <85 mm Hg	DBP ≥85 mm Hg	All Subjects	DBP <85 mm Hg	DBP ≥85 mm Hg
Age (years)	−0.60*	−0.60†	−0.54†	−0.51*	−0.50‡	−0.44‡
DBP (mm Hg)	−0.44*	0.30	0.06	−0.31‡	0.25	0.24
SBP (mm Hg)	0.0	0.38	0.06	0.14	0.30	0.15
MAP (mm Hg)	−0.30‡	0.10	0.01	0.15	0.15	0.21
PP (mm Hg)	+0.32‡	0.43‡	0.12	+0.38†	+0.47‡	0.05
HR (bpm)	0.22	0.20	−0.42‡	−0.28‡	0.20	−0.45‡
DBP variability (mm Hg)	0.19	0.29	0.0	0.37†	0.45‡	0.24
HR variability (bpm)	0.35‡	0.33	0.19	0.30*	0.24	0.20

For abbreviations, see Tables 2 and 3.

**P < .001; †P < .01; ‡P < .05.*

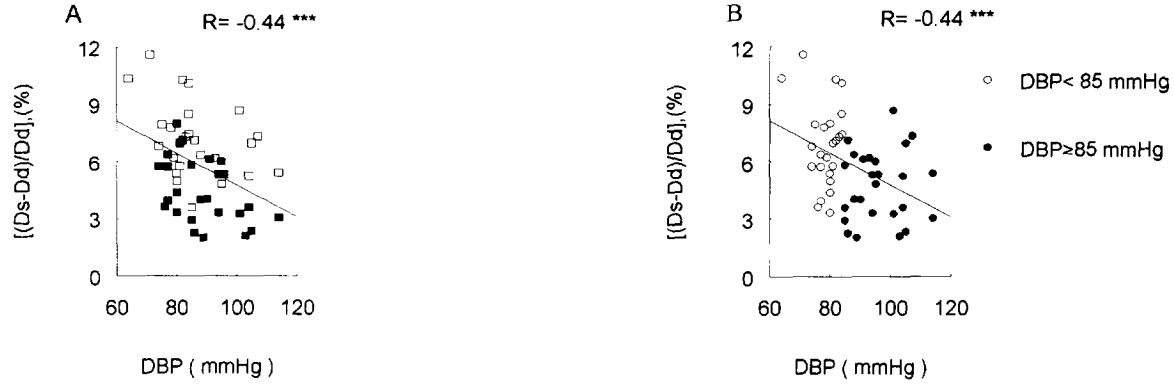

FIGURE 1. *Correlations between diastolic blood pressure and the relative stroke change in carotid diameter. Effects of age (A) and hypertension (B). Note that for a given DBP [(Ds − Dd)/Dd] is higher in younger than in older subjects.* ***P < .001. *A: Open boxes, age < 45 years; filled boxes, age ≥ 45 years.*

er age, hypertension, or the combination of both factors has the most important influence on the arterial wall. Recent studies have shown that the mechanical properties of the peripheral arteries, such as the radial artery, are poorly influenced by age, whereas those of the central arteries, such as the carotid artery, are predominantly influenced by age.[19] In the present study, using a stepwise regression analysis, we showed that, independently of age, the carotid distension was significantly influenced by several mechanical parameters evaluated from the characteristics of the blood pressure curve. More specifically, it appeared that not only the levels of systolic and diastolic pressure have to be analyzed in hypertension, but also the levels of pulse pressure and heart rate. Such findings were obtained from new techniques permitting evaluation of the pulsatile changes in diameter and blood pressure.

In recent years, several devices have been described that transcutaneously measure arterial diameter and wall motion by tracking the echo signals from both the anterior and posterior walls.[11–14] The device used in the present study was substantially improved with the help of the Doppler shift to evaluate wall motion,[11] thus permitting a high degree of reproducibility for the determination of the distension capacity of the carotid artery. In this respect, the observed values in subjects with DBP < 85 mm Hg and in subjects with DBP ≥ 85 mm Hg were quite similar to those previously reported.[13,14,19,20]

In contrast to the measurement of carotid arterial distension, the mechanical signal responsible for the

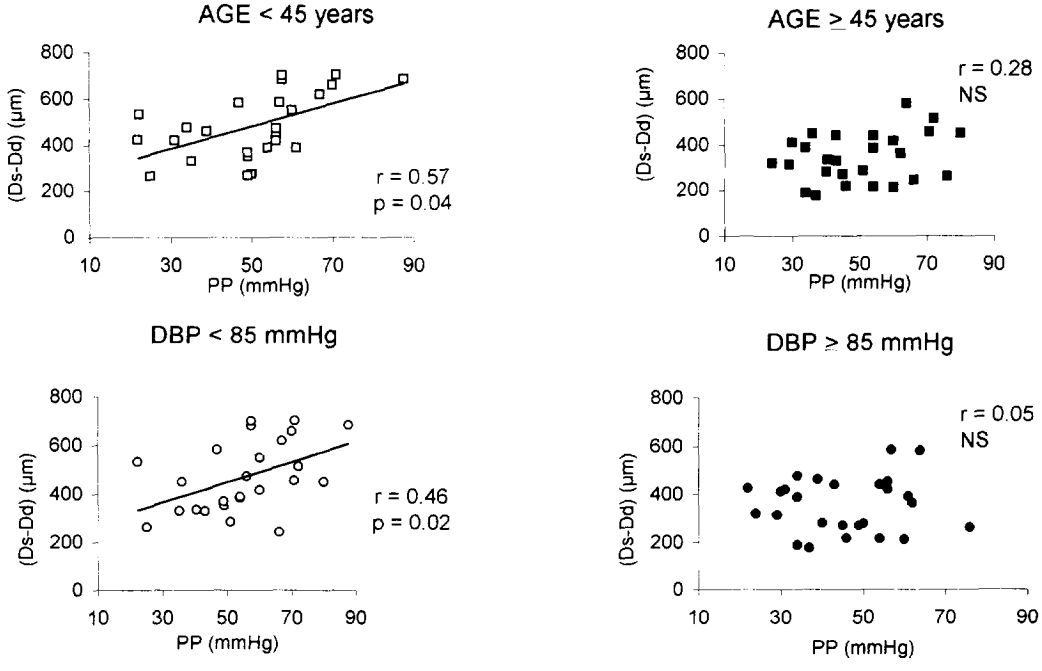

FIGURE 2. *Influence of age and diastolic blood pressure on the correlation between absolute carotid distension and pulse pressure.*

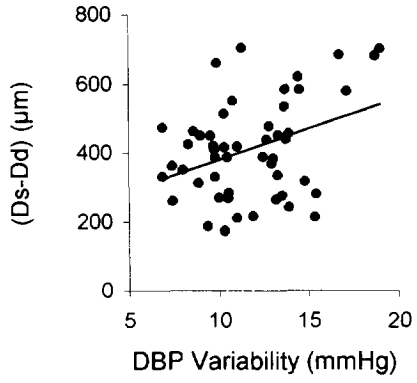

FIGURE 3. *Correlation between absolute carotid distension (Ds − Dd) and DBP variability. r = 0.37; P = .008.*

pulsatile change in diameter, ie, carotid pulse pressure, is much more difficult to obtain in clinical practice for two reasons. First, a noninvasive determination of carotid blood pressure, as usually obtained by applanation tonometry, requires a calibration of the pressure curve, an estimation that reduces the reproducibility of the method.[10,19] Second, pulse pressure varies greatly along the arterial tree, with a lower amplitude in the central than in the peripheral arteries.[10] Thus carotid pulse pressure is difficult to evaluate from the simple measurement of brachial pulse pressure. For such reasons, the present work was limited to the study of the relationships between the distension capacity of the common carotid artery and the brachial blood pressure measurements obtained from ambulatory monitoring. Even considering that this approach cannot support the presumption of a causal relationship between blood pressure parameters and the carotid arterial distension, the described methodology has definite advantages. First, the mean value of serial blood pressure measurements is known to give a better insight into the average baseline level and the variability of blood pressure than casual blood pressure, as shown in the present study and previously reported results.[6,7] Second, in this study, the ambulatory blood pressure determinations were not restricted to the measurements of systolic, diastolic, or mean arterial pressure, but also involved the calculation of pulse pressure. As shown previously,[17,21] pulse pressure is poorly correlated with the mean arterial pressure in a given population and was even slightly lower in the subjects with DBP ≥ 85 mm Hg. Finally, multiple ambulatory blood pressure measurements have been shown to be more significantly related than casual blood pressure to the most classical indexes of arterial stiffness, such as pulse wave velocity.[21]

In the present study, a positive correlation was observed in the totality of the population between brachial pulse pressure and the carotid distension capa-

TABLE 5. RESULTS OF A FORWARD STEPWISE MULTIPLE REGRESSION OF FACTORS INFLUENCING CAROTID PARAMETERS

Dependent Variable: [(Ds − Dd)/Dd]; n = 51; multiple R = 0.75					
Variable	**Coefficient**	**Standard Error**	**Standard Coefficient**	**T**	***P*(Two-tail)**
Constant	18.76	2.71	0.000	6.90	.000
Age	−0.094	0.017	0.535	−5.15	.000
DBP	−0.06	0.019	−0.310	−3.1	.003
PP	0.031	0.014	0.210	2.14	.037
HR	−0.059	0.02	−0.285	−2.97	.005
Analysis of variance: F-ratio = 15.26 *P* = .000					
Dependent Variable: Ds − Dd; n = 51; multiple R = 0.75					
Variable	**Coefficient**	**Standard Error**	**Standard Coefficient**	**T**	***P*(Two-tail)**
Constant	902.83	175.24	0.000	5.15	.000
Age	−4.46	1.09	−0.413	−4.09	.000
PP	2.50	0.916	0.275	2.73	.009
HR	−4.16	1.24	−0.365	−3.7	.001
DBP variability	13.82	4.92	0.284	2.8	.007
Analysis of variance: F-ratio = 12.30 *P* = .000					

For abbreviations see Table 2.

Coefficient reflects the correlation between predictors.

Standard Error, expected error using these predictors in other group.

Standard Coefficient, relative contribution of the predictors to the model.

city measured either in absolute or relative values. This finding supports the well-established concept that the principle mechanical factor causing the stroke change in arterial diameter in animals and humans is pulse pressure. However, this correlation was found to be stronger in younger subjects or in those with DBP < 85 mm Hg, rather than in older subjects or those with DBP ≥ 85 mm Hg. This finding is difficult to explain. Physiologically, the pressure-diameter relationship is known to be nonlinear and involves two different phases;[10] in the lower pressure ranges, the slope of the curve is steeper because blood pressure bears mainly on the elastin fibers and the vascular smooth muscle of the arterial wall. In the higher pressure ranges, the slope of the curve is flatter, since blood pressure bears almost exclusively on collagen fibers. Since the collagen content of the arterial wall increases with age and level of blood pressure, the latter situation is known to be observed particularly in older and hypertensive subjects, thus leading to insignificant values of correlation coefficients for the curve relating pulsatile pressure to pulsatile diameter (Figure 2). In our study, the finding that the distension capacities were negatively influenced by the baseline average level of diastolic blood pressure corroborates this interpretation. In subjects with the lower baseline diastolic pressure ranges, the correlation between pulsatile pressure and pulsatile diameter is significant, whereas the significance of the correlation disappears in the higher baseline diastolic pressure ranges, thus indicating a flatter curve. In the study of this relationship, not only the correlation coefficients were predominantly significant in the younger subjects and in populations with DBP < 85 mm Hg, but the level of the correlation coefficients was also relatively low. This finding raises the question of the numerous factors (other than pulse pressure) which could modulate the distension capacities of the carotid artery. In this regard, age is certainly of major importance. It is the cumulative effect of the increasing values pulse pressure with increasing age which should be important to consider for arterial thickening and damage. However, this factor is difficult to estimate in the present statistical evaluation.[19] On the other hand, pulsatile pressure and, moreover, pulsatile blood flow may alter the arterial wall and cause structural changes through both mechanical and nonmechanical factors involving the transducer properties of the endothelium.[22] Endothelium, through the release of vasoactive substances, may modify the distension capacity of the arteries, as shown from experimental studies in rats.[23] These vasoactive properties are strongly influenced by age.[22] Therefore, at any given value of pulse pressure, changes in endothelium function may greatly influence the distension capacity of the carotid artery. Such observations are important to consider since pulse pressure in humans is an important independent cardiovascular risk factor,[2,3] with several implications involving the pathology of the heart[24,25] and the vessels[26–28] in older people.

In the present study, the distension capacity of the carotid artery was influenced not only by the average level of baseline diastolic blood pressure but also by the variability of this parameter. For a given value of diastolic blood pressure, the distension capacity of the carotid artery was positively associated with diastolic blood pressure variability. In recent years, few studies have reported that blood pressure variability may interact with the distension capacities of the arterial wall. In populations of hypertensive subjects, Parati et al[6] and Frattola et al[7] have shown that end-organ damage for long term follow-up was related not only to the level of clinic blood pressure and the initial level of end-organ damage but also to long-term blood pressure variability at the initial evaluation. On the other hand, Lacolley et al[29] described an experimental model in rats in which blood pressure variability was selectively increased in the absence of any significant change in systolic, diastolic, or mean arterial pressure. In this study increased blood pressure variability was not associated with a substantial change in operational carotid distension. Whether this observation, done as a longitudinal study, is relevant for the present human cross-sectional approach remains to be explored.

The most important finding of this study was that, independently of blood pressure changes, the distension capacity of the carotid artery was negatively associated with heart rate: the higher the heart rate, the more reduced the R-R interval and the lower the carotid capacity for distension. Because the viscous component of the carotid arterial wall is known to be highly frequency dependent, it is expected that the higher values of heart rates might be associated with the more reduced capacity for distension.[30–32] Thus, for a given value of pulse pressure, arterial stiffness (ie, the ratio between the distension capacity and pulse pressure) is expected to be higher when the heart rate is increased, a finding reported previously.[21] This frequency dependence of the various indices of arterial stiffness has been described previously in several experimental studies[10] but becomes particularly important to evaluate in human populations because: i) numerous epidemiologic reports have emphasized that elevated heart rate is associated with an increased occurrence of clinical cardiovascular morbid events,[4,5] ii) it has been established that cycling stretching stimulates synthesis of matrix components by arterial smooth muscle cells in vitro,[31] and iii) experimental studies in atherosclerotic monkeys have shown that increased heart rate through

disturbed shear stress is positively correlated with plaque formation at the site of the carotid bifurcation.[32–34] Taken together, such observations raise the possible role of the activation of the autonomic nervous system in the mechanisms of the distension capacity of the carotid artery. The autonomic nervous system may modulate not only the average heart rate over 24 h but also the amplitude of minute-to-minute excursions in heart rate and the time necessary for heart rate to return to baseline following various changes in 24-h activity. In that condition, it is relevant to notice that, in the present study, the distension capacity of the carotid artery was influenced not only by the average baseline level of heart rate but also by the 24-h heart rate variability.

Some findings of the present study should be considered with caution. Indeed, studies of pulsatile arterial hemodynamics indicate that, as arteries stiffen and become less distensible, pulse wave velocity increases, systolic blood pressure increases, diastolic blood pressure decreases, and pulse pressure widens. Thus one might expect a direct relation between diastolic blood pressure and distensibility in older individuals with predominant systolic hypertension and an inverse relation between the two in predominant diastolic hypertension (and the inverse for pulse pressure). However, such findings would be expected principally from a longitudinal study and do not disagree with the present cross-sectional investigation in which the younger and older subjects had a narrow difference between their mean age (36 and 56 years, respectively). In our comments we have shown under what conditions the present methodology agrees with several aspects of pulsatile arterial hemodynamics, and that it largely concords with the curvilinearity of the pressure-diameter relationship.

In conclusion, the present study has shown that the distensions capacity of the carotid artery is modulated in humans not only by the level of systolic or diastolic blood pressure but also by several other mechanical signals estimated from the blood pressure curve: the elevation of pulse pressure, the increase in the variability of blood pressure, and the increased level and variability of heart rate. All these mechanical signals may act independently on the arterial wall, and, moreover, independently of age, as shown from the stepwise multiple regression analysis (Table 5). Furthermore, in addition to the level of systolic and diastolic blood pressure, increased pulse pressure and elevated heart rate are known to be independent factors of cardiovascular risk.[2–5] In the present study, it is shown that, for a given pulse pressure, the carotid artery is more rigid with an elevated than with a low heart rate. Whether these arterial changes participate in target organ damage and therefore in cardiovascular morbidity and mortality has never been explored in animals and humans and remains to be investigated.

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