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Aortic Distensibility in Normotensive, Untreated and Treated Hypertensive Patients

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Background: Compared with normotensive subjects, untreated hypertensive patients show a decrease of their aortic distensibility. Whether antihypertensive treatment, by reducing blood pressure and changing functional and/or structural abnormalities of the arterial wall, may prevent or reverse the arterial damage due to the accelerated ageing process remains unclear. The objective of the present study was to determine, using a cross-sectional approach, whether aortic distensibility as measured by pulse wave velocity, in treated hypertensive patients whose diastolic blood pressure had been normalised for several months, was significantly improved over that of untreated hypertensive patients.

Methods: Carotid femoral pulse wave velocity was measured in 124 normotensive subjects and 388 hypertensive patients. The latter group included 164 treated patients with well controlled diastolic blood pressure and 224 untreated hypertensive subjects. The three groups did not differ in other cardiovascular risk factors.

Results: In each group there was a significant relationship between age and pulse wave velocity. When compared with untreated hypertensives, treated hypertensives with well controlled diastolic blood pressure had significantly lower blood pressure and pulse wave velocity according to age. However, although diastolic blood pressure of well controlled hypertensives was not significantly different from that of normotensive subjects, the aortic distensibility of the controlled hypertensives remained reduced showing two characteristics: a faster increase in pulse wave velocity with age and a negative relationship with HDL-cholesterol.

Conclusion: These results suggest that long-term antihypertensive treatment and control of blood pressure using only diastolic blood pressure criteria may not fully reverse arterial alteration associated with hypertensive vascular disease. *Key words: antihypertensive agents, arterial distensibility, pulse wave velocity, cardiovascular risk factors.*

INTRODUCTION

Damage to large arteries is a major contributing factor to the elevated cardiovascular morbidity and mortality observed in hypertension [1]. Reduced arterial distensibility in hypertension contributes to a disproportionate increase in systolic pressure and to an increase in pulse pressure at any given value of mean arterial pressure [2]. The increase in pulse pressure has been shown to be associated with an increase in cardiovascular morbidity and mortality [3, 4]. Antihypertensive treatment, by lowering blood pressure and correcting some functional and/or structural abnormalities of the cardiovascular system [5–7], should prevent cardiovascular damage and reduce the accelerated ageing process resulting from high blood pressure [8,9].

Quantitative information on the function of large arteries may be commonly obtained by determination of pulse wave velocity. Both pulse transducer or continuous Doppler procedures are widely used to evaluate indirectly arterial distensibility [2, 9–11]. Recent progress in non-invasive techniques enable measurement of this variable with a high degree of reproducibility [2, 9, 11]. In the present cross-sectional study, we compared aortic distensibility in normotensive subjects, untreated hypertensive patients, and well-controlled hypertensive patients on antihypertensive treatment. These two groups of hypertensive patients were selected from the population of our out-patient clinic in order to determine whether arterial distensibility of patients whose diastolic blood pressure had been normalised for a long period by antihypertensive treatment was significantly improved over that of untreated patients, and if it ranged within normal values. This cross-sectional approach should provide data to answer the following question: By normalising diastolic blood pressure (below 90 mmHg) of hypertensive patients over a long period of time, do we also normalise the buffering function of large arteries?

MATERIAL AND METHODS

Patients

Five hundred and twelve subjects entered this study. They were divided in three different groups: normotensive controls (group I), untreated hypertensive patients (group II) and treated hypertensive patients with well controlled diastolic blood pressure (group III). Their clinical characteristics and cardiovascular risk factors are shown in Table I.

Normotensive controls—Group I: One hundred and

Table I. *Clinical and biological characteristics*
± 1 standard deviation.

Group I: normotensive patients. Group II: untreated hypertensive patients. Group III: treated with well controlled diastolic BP.

	Group I (n = 124)	Group II (n = 224)	Group III (n = 164)	F	p values
Age range (years)	45 ± 13	48 ± 11	59 ± 11	79	< 0.0001
Weight (kg)	67 ± 12	73 ± 12	72 ± 14	9.8	= 0.0001
Systolic blood pressure (mmHg)	125 ± 9	164 ± 13	144 ± 18	178	< 0.0001
Diastolic blood pressure (mmHg)	77 ± 8	102 ± 9	82 ± 7	348	< 0.0001
Plasma glucose (mmol/l)	5.6 ± 1.9	5.8 ± 0.9	6.1 ± 1.6	1.14	NS
Plasma cholesterol (mmol/l)	5.8 ± 1.1	6.0 ± 1.0	5.9 ± 1.1	0.40	NS
Plasma HDL-cholesterol (mmol/l)	1.4 ± 0.3	1.6 ± 0.4	1.4 ± 0.4	4.3	NS
Tobacco consumption (packets/year)	5 ± 13	6 ± 14	5 ± 13	0.06	NS
Pulse wave velocity (m/s)	8.5 ± 1.5	11.8 ± 2.7	10.1 ± 2.6	86	< 0.0001

twenty-four normal subjects were analysed in this group. They had no previous personal or hereditary cardiovascular disease. They were either normal volunteers or recruited from several systematic health follow-up centers (Labour Health Division, Army Medical Supervision) and a Geriatric Department. There were 73 males and 51 females, aged from 18 to 77 years.

Untreated hypertensive patients—Group II: Two hundred and twenty- four hypertensive patients aged from 18 to 81 years were included in this group. All of them had essential, uncomplicated hypertension which was defined as mild to moderate on the basis of diastolic blood pressure measured in the supine position with an average of 3 casual measurements from 95 to 114 mmHg. Secondary hypertension was excluded on the basis of classical laboratory tests [7]. None of the patients had cardiac, neurological or renal involvement or arteriopathy of the lower limbs. Patients with valvular heart disease, arrhythmia or carotid artery stenosis were excluded from the study. They had never been treated, or treated for less than 3 months and had discontinued treatment at least 1 month before. The mean duration of their hypertension, as determined from the patients' file, was 3.8 ± 5 years (mean ± SD). Serum glucose, total cholesterol and HDL cholesterol were measured on the day of the haemodynamic study.

Drug treated hypertensive patients with well controlled diastolic blood pressure—Group III: One hundred and sixty-four hypertensive patients aged from 27 to 81 years were included in this group. All of them were treated and classified as well controlled by antihypertensive treatment (whatever their treatment) if their diastolic blood pressure had been below 90 mmHg during the 3 months preceding the study. The mean duration of the hypertensive disease, as determined from the patients' files, was 5.6 ± 4.8 years (mean ± SD). The mean duration of their treatment was 4.7 ± 4.3 years (mean ± SD). The mean duration of normalised diastolic blood pressure was 3.9 ± 4.1 years. At the time of the study, 37% of the patients were treated by monotherapy, 32% by bitherapy and 31% by tri- or multiple therapy. Drugs are indicated below. Values of biological cardiovascular risk factors were those of the haemodynamic day (Table I).

Study design

Investigations were performed in a controlled environment kept at 21 ± 2°C. Blood pressure was measured using a mercury sphygmomanometer with cuff adapted to arm circumference after the subjects had been recumbent for at least 15 min. Systolic blood pressure was taken as the point of appearance of Korotkoff sounds (phase 1) and diastolic blood pressure as the point of their disappearance (phase 5).

For the determination of pulse wave velocity (PWV), two different Doppler flow recordings were obtained at two sites [2, 11]: at the base of the neck for the common carotid artery and over the right femoral artery. Flow was measured with a continuous Doppler unit (SEGA-M842, Oregon, USA) with handheld probes. Transcutaneous Doppler flow waves were recorded simultaneously with two electrocardiogram leads on a paper recorder at high speed (150 mm/s). Pulse wave velocity was determined as foot to foot velocity. The foot of flow wave was identified as the point of the beginning at the sharp systolic upstroke. When this point could not be identified precisely, a tangent was drawn to the last part of the preceding flow wave and to the upstroke of the next wave, and the foot wave was taken as the point of intersection of these two lines. The time delay was measured between the feet of the flow waves and the electrocardiographic signal recorded simultaneously with each of these

different flow waves. The average of 10 consecutive beats was taken as pulse transit time, and the mean value of two different observers' determinations was taken for statistical analysis. The distance travelled by the pulse wave was measured over the body surface as the distance between the two recording sites (carotid and femoral); the distance from the carotid site to the aortic arch was not subtracted from the total distance; this may provide slightly higher values of PWV but approximate measurements are avoided. Arterial pulse wave velocity was calculated as the ratio between distance and transit time. The reproducibility of the measurement for aortic PWV (expressed as % variation of the mean value) was $5.3 \pm 3.6\%$, as has been previously reported [11].

For the validation of PWV, as an index of arterial distensibility and stiffness, it is important to recall that the pressure or flow wave generated by ventricular ejection is propagated throughout the arterial tree. Since the blood is contained in a system of elastic conduits, energy propagation occurs along the distensible artery wall and not through the incompressible blood. The elastic properties of the arterial wall, its thickness and the diameter are the major determinants of the speed of propagation of the pulse wave, which determines vascular impedance and total opposition to pulsatile flow [2]. These concepts have been formalised in mathematical models. For large arteries, the most widely accepted relationship of PWV and elastic modulus (E) is given by the Moens-Korteweg equation [2].

$$PWV = (Eh/2r\ m)^{1/2}$$

where E = Young's modulus of the wall; h = wall thickness; r = vessel radius; m = blood density. Hence, valuable information on aortic distensibility and stiffness can be determined noninvasively as regional PWV, which is an index of arterial distensibility (the higher the PWV, the lower the arterial distensibility).

Statistical analysis [12]

Statistical analysis was performed with NCSS® statistical software (Kaysville, Utah, USA). Values are expressed as mean ± standard deviation. Descriptive tests were used to express the range values and to analyse the distribution homogeneity of the population. Comparison of the mean values of the three groups was performed using a one way analysis of variance (ANOVA). Comparison of the qualitative variables was performed using the Chi^2 Test. A simple regression test was performed to analyse the linear correlations between two parameters. A multiple regression test was used to analyse the simple and partial linear correlation between more than two parameters. Comparison between two regressions was performed using the unpaired Student's *t* test to analyse the slopes, and the covariance analysis to study the intercepts. The significance level was set at 0.05.

RESULTS

Normotensive subjects (Group I). Fig. 1 shows in normotensive subjects (Group I) a positive relationship between pulse wave velocity and age ($r = 0.55$; $y = 0.0628\ x + 5.728$; $p < 0.001$). Thus, a normogram with individual and mean 95% confidence limits could be defined. Mean value of pulse wave velocity in Group I was 8.5 ± 1.5 m/s.

Untreated hypertensive patients (Group II). Mean value of pulse wave velocity in Group II (untreated hypertensive subjects) was 11.8 ± 2.7 m/s. Fig. 2 shows the relationship between pulse wave velocity and age in Group II ($r = 0.48$; $y = 0.123\ x + 6.27$, $p < 0.001$). The comparison between the hypertensive and normotensive relationships of PWV with age shows that, at any given age, PWV was significantly higher in Group II by comparison with Group I ($p < 0.001$). Multiple regression analysis indicated that only two factors influenced pulse wave velocity in hypertensives: systolic blood pressure ($p < 0.001$) and age ($p < 0.01$). Sex, weight, tobacco consumption, plasma glucose, cholesterol, and HDL-cholesterol did not significantly influence this variable.

Treated subjects with well controlled diastolic blood pressure—(Group III). Mean value of pulse wave velocity in treated subjects with diastolic BP < 90 mmHg (Group III) was 10.1 ± 2.6 m/s. Fig. 3 shows the relationship between pulse wave velocity and age in Group III ($r = 0.48$; $y = 0.110\ x + 3.464$; $p < 0.001$). By comparison with Group I, patients of Group III had a significantly steeper slope ($p < 0.01$), indicating that, despite an adequate control of diastolic blood pressure, pulse wave velocity increased more with age in Group III than in Group I. In well controlled hypertensives of Group III, three factors influenced pulse wave velocity on the basis of multiple regression analysis: age ($p < 0.001$), systolic blood pressure ($p < 0.05$) and low HDL cholesterol ($p < 0.05$).

To analyse the role of controlling diastolic alone or with systolic blood pressure on pulse wave velocity, patients of Group III were divided into two subgroups: in subgroup A, both diastolic (< 90 mmHg) and systolic (≤ 140 mmHg) were controlled; in subgroup B, diastolic blood pressure was controlled (< 90 mmHg) but systolic blood pressure was uncontrolled (> 140 mmHg). Table II shows that the two subgroups (A and B) differed by age (57 ± 11 vs 62 ± 10 years; $p < 0.002$); and by the value of pulse

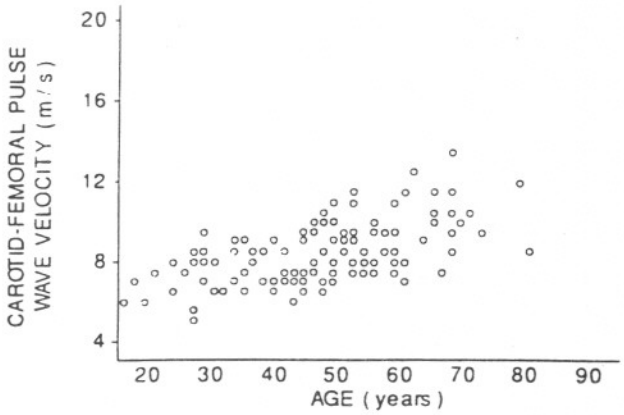

Fig. 1. Carotid-femoral pulse wave velocity: relationship with age in normal subjects (group I).

wave velocity (9.3 ± 2.3 vs 10.9 ± 2.7 m/s; $p < 0.0001$). However, even when age was taken as covariate, pulse wave velocity remained higher in subgroup B ($F = 8.11$; $p = 0.005$). Fig. 3 shows the plot of pulse wave velocity with age in subgroups A and B; whereas the relationship did not differ between Group I and subgroup A, pulse wave velocity increased more markedly with age in subgroup B ($F = 10.63$; $p = 0.001$). In this subgroup, the HDL cholesterol value did not influence pulse wave velocity (multiple regression analysis) whereas it did so in subgroup A. Table III indicates that the distribution of drug treatment did not differ between subgroups A and B.

DISCUSSION

The present cross-sectional study was performed in order to determine whether aortic distensibility of patients whose diastolic blood pressure had been normalised for several months by antihypertensive treatment was significantly improved and ranged within normal values. Aortic distensibility was assessed non-invasively using carotid-femoral pulse wave velocity.

Relationship between pulse wave velocity and age in normotensive and hypertensive subjects. The most important factor contributing to increased pulse wave velocity in human populations is age [2]. This is attributed to increased arterial stiffness because of medial calcification and loss of elasticity with age. In addition to the role of age, pulse wave velocity also depends on the level of blood pressure: the higher the pressure, the faster the speed of wave travel. This is due to the increase in the elastic modulus of the arterial wall with circumferential tension. Such mechanisms, which have been widely studied [2, 6, 9, 13, 14], above all have an effect in the aorta, due to its predominant visco-elastic properties.

In the present study, both the role of age and blood pressure on pulse wave velocity could be assessed very simply using a normogram relating pulse wave velocity to age. In untreated hypertensive subjects, pulse wave velocity was significantly higher than in normotensive controls at any given value of age. In treated, with diastolic well controlled hypertensive patients (Group III), pulse wave velocity returned toward the confidence limits of the normotensive values but two particularities remain to be discussed. First, pulse wave velocity increased with age faster than in normotensive controls. This trend has also recently been reported for the distensibility of the common carotid artery [15]. Secondly, following treatment, the lowering of HDL-cholesterol became a significant factor influencing pulse wave velocity, together with age and blood pressure.

Faster increase in pulse wave velocity with age in well controlled hypertensive patients. Due to the disparity within the treatment group regarding the form and duration of treatment, we should consider these results as preliminary data. If they were to be confirmed, mainly by a longitudinal study, it would be necessary to understand why aortic stiffness may not be normalised in hypertensive patients despite long-term control of diastolic blood pressure by treatment. Pharmacological studies suggest that not all antihypertensive treatments improve arterial compliance and stiffness. Indeed, the potassium-sparing diuretic canrenone [16], the potassium non-sparing diuretic indapamide [17], the beta-adrenergic-blocking agent propranolol, the arteriolar vasodilator dihydralazine and the alpha-adrenergic-blocking agent urapidil [18] were shown not to change arterial compliance, in contrast with the calcium antagonists nicardipine, nifedipine and nitrendipine and the converting enzyme inhibitors captopril, enalapril and perindopril [18]. These results, obtained principally at the level of the brachial artery from measurements of brachio-radial pulse wave velocity and brachial artery cross-sectional area [7], were consistent with the improvement in distensibility observed in Group III and with the finding by Van Merode et al. [19] about carotid compliance. Therefore, the antihypertensive treatment used in Group III may have included agents improving arterial compliance together with the decrease in distending pressure.

In the present study, the subdivision of the well-controlled hypertensive patients into those with both adequate control of systolic and diastolic blood pressure (subgroup A) and those with adequate control of diastolic blood pressure but uncontrolled systolic

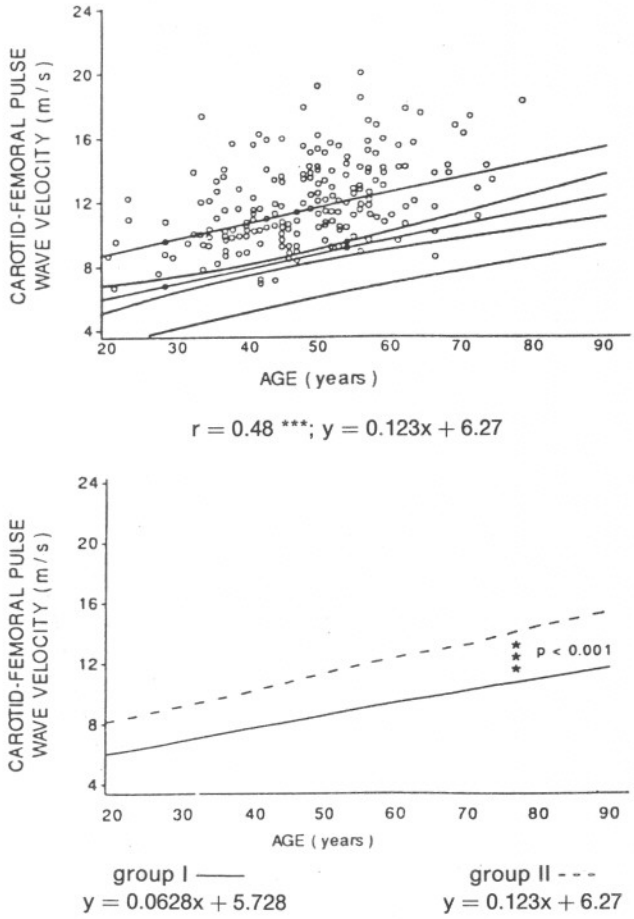

Fig. 2. Carotid-femoral pulse wave velocity (y): relationship with age (x) in untreated hypertensive subjects (Group II). Plot of hypertensive patients by comparison with the normotensive normogram (with its individual and mean 95% confidence limits). The lower part compares the normotensive (——) and the hypertensive (- - - - -) curves.

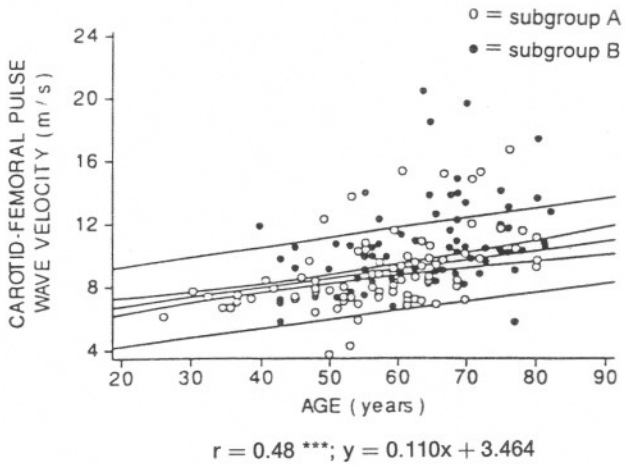

Fig. 3. Carotid-femoral pulse wave velocity (y): relationship with age (x) in well controlled hypertensive subjects (Group III). Plot of the group III by comparison with the normotensive normogram and its individual and mean 95% confidence limits. ○ = subgroup A, diastolic BP < 90 mmHg and systolic BP < 140 mmHg; ● = subgroup B, diastolic BP < 90 mmHg and systolic BP > 140 mmHg.

blood pressure (subgroup B) indirectly reveals the role of antihypertensive drug treatment. Indeed, the mean duration of hypertension, its treatment and the distribution of drugs were identical in subgroups A and B (Table III) whereas pulse wave velocity was more substantially increased in subgroup B, a finding observed even after adjustment for age. From these findings, the mechanisms that may underlie the accelerated pulse wave velocity in subgroup B cannot be recognised. Nevertheless, the proposed classification into subgroups A and B emphasises the point that the exclusive choice of diastolic blood pressure for the evaluation of drug treatment is inadequate. Indeed, an elevated proportion of patients at cardiovascular risk (with uncontrolled systolic pressure but controlled diastolic pressure) is dismissed when the diastolic pressure criterion only is used [20]. This methodological aspect may be one explanation for the lack of prevention of coronary ischaemic accidents following large therapeutic trials in hypertension [20, 21]. Thus controlling BP using standard criteria based on only diastolic pressure may not be sufficient to prevent vascular abnormalities observed in hypertension.

HDL-cholesterol as a factor influencing pulse wave velocity in well-controlled hypertensive subjects. There are conflicting reports on the relationship of lipid abnormalities with the stiffening of large arteries in man. Reduced arterial compliance and higher values of pulse wave velocity in non-occluded arteries have been demonstrated in patients with coronary artery disease and in patients with diabetes mellitus [22, 23]. Other studies have shown no significant differences in changes in pulse wave velocity with age in subjects with a high risk of atherosclerosis, such as familial hypercholesterolemia, or in populations with different prevalences of atherosclerosis such as Western and Asian populations [24, 25]. Furthermore, studies of large groups of Chinese and German populations have failed to demonstrate any association between pulse wave velocity and total plasma cholesterol [25, 26]. However, in such investigations, the different fractions of lipoproteins were not widely evaluated. In a study on the relationship between lipid fractions and aortic pulse wave velocity, Relf and al. [27] and London and al. [11] found an inverse weak correlation between HDL-cholesterol and aortic pulse wave velocity but no significant correlation with total plasma cholesterol. In the present study, a significant relationship was observed between pulse wave velocity and HDL-

Table II. *Clinical and biological characteristics of treated patients with well-controlled diastolic BP (Group III): subdivided into two subgroups A and B (± 1 S.D.)*

Subgroup A: Systolic and diastolic blood pressure are controlled (< 140 and < 90 mmHg respectively).
Subgroup B: Diastolic blood pressure is controlled (< 90 mmHg) but systolic blood pressure is uncontrolled (> 140 mmHg).

	Subgroup A ($n = 86$)	Subgroup B ($n = 78$)	p values
Age range (years)	57 ± 11	62 ± 10	< 0.002
Weight (kg)	73 ± 13	71 ± 15	NS
Systolic blood pressure (mmHg)	130 ± 7	158 ± 13	< 0.0001
Diastolic blood pressure (mmHg)	80 ± 7	84 ± 7	< 0.01
Plasma glucose (mmol/l)	5.9 ± 1.7	6.1 ± 1.4	NS
Plasma cholesterol (mmol/l)	5.8 ± 1.0	6.1 ± 1.2	NS
Plasma HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.5 ± 0.4	0.05
Tobacco consumption (packets/year)	5 ± 10	6 ± 15	NS
Pulse wave velocity (m/s)	9.3 ± 2.3	10.9 ± 2.7	0.001

cholesterol, but it was limited to a population of treated well-controlled hypertensive subjects.

Pharmacological studies suggest that some antihypertensive drugs such as certain diuretics and beta-blocking drugs tend to decrease HDL-cholesterol whereas an improvement of plasma-lipoproteins may be obtained with alpha-blocking agents [28]. In the present investigation, the subdivision of well controlled hypertensive subjects into subgroups A and B did not suggest an important role of drug treatment as a factor influencing the relationship between pulse wave velocity and HDL-cholesterol. Indeed, the repartition of drugs was quite similar in subgroups A and B (Table III) whereas the influence of HDL-cholesterol on pulse wave velocity was observed only in group A. This complex relationships between lipoproteins and arterial stiffness cannot be completely resolved from the present study, although the structural changes of the vessels associated with increased stiffness may be the basis for a disturbance of the lipoprotein clearance as commonly observed within the hypertensive arterial wall [29].

Limitations of the study. First it should be stressed that a longitudinal study is required to conclude on the contribution of antihypertensive treatment in changes of aortic stiffness.

Secondly, there is an obvious disparity within the treatment groups as to the form and the duration of treatment. The uncontrolled nature of the antihypertensive treatment is due to the cross-sectional nature of the study, some patients being controlled for a long time with classic medication such as diuretics and/or beta-blockers, whereas more recently diagnosed hypertensives were treated with other medications such as calcium antagonists and/or converting enzyme inhibitors.

Thirdly, pulse wave velocity was used as a marker of arterial stiffness. For a thin arterial wall, this variable is influenced by at least three different factors: aortic diastolic diameter, systolic-diastolic variation of arterial diameter and aortic pulse pressure. In untreated hypertensive subjects, aortic diastolic diameter is known to be increased, systolic-diastolic variations of arterial diameter to be decreased and pulse pressure to be increased [13, 14]. Following antihypertensive treatment, changes of each of these variables could not be directly evaluated. In particular, the decrease in pulse pressure following drug treatment may be even more pronounced at the site of the aorta than at the site of the brachial artery, whereas the decrease in mean arterial pressure is known to be nearly the same [2]. However, this dissociation is observed preferentially in younger subjects since the amplification of the pressure wave between the aortic and the brachial artery is known to decrease with age.

In conclusion, despite an adequate normalisation of diastolic blood pressure, antihypertensive drug treatment involves aortic changes associating an accelerated increase of arterial stiffness with age and a more pronounced influence of plasma HDL-cholesterol on arterial stiffness. Longitudinal studies using more specific drug treatment are needed in order to determine whether arterial stiffness remains altered despite long-term control of blood pressure and whether this is

Table III. *Distribution of anthihypertensive drugs: Subdivision of well-controlled hypertensive subjects (Group III) into subgroups A and B (see Table II)*

	Subgroup A	Subgroup B
Beta blocking agents	11.6%	10.1%
Diuretics	17.9%	16.4%
Converting enzyme inhibitors	9.7%	11.1%
Calcium entry blockers	9.2%	9.2%
Others	1.9%	2.9%

due to the quality of antihypertensive treatment or to the hypertensive disease *per se*.

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