

Arterial distensibility in subjects with white-coat hypertension with and without diabetes or dyslipidaemia: comparison with normotensives and sustained hypertensives

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Background Arterial distensibility can be assessed by measuring pulse-wave velocity (PWV).

Objective To determine whether diabetes, smoking and dyslipidaemia were associated with greater than normal stiffness of aortic walls in subjects with white-coat hypertension.

Methods Arterial distensibility was assessed by automatic measurement of carotid-femoral PWV in 35 healthy normotensives, 46 white-coat hypertensives (WCH, clinic blood pressures > 140/90 mmHg, daytime blood pressures < 130/85 mmHg) and 81 ambulatory hypertensives (clinic blood pressures > 140/90 mmHg, daytime blood pressures \geq 130 mmHg systolic or \geq 85 mmHg diastolic, or both) all matched for age, sex and body mass index. Nineteen normotensives (subgroup A), 28 WCH (subgroup A) and 37 ambulatory hypertensives (subgroup A) had only one or no other major cardiovascular risk factor whereas 16 normotensives (subgroup B), 18 WCH (subgroup B) and 44 ambulatory hypertensives (subgroup B) had also some combination of non-insulin-dependent diabetes, a smoking habit and dyslipidaemia.

Results Both for the WCH and for ambulatory hypertensives diabetes and dyslipidaemia (subgroups B) were associated with higher ($P < 0.04$) PWV (11.6 ± 0.3 and 12.8 ± 0.3 m/s, respectively) than for subgroups A (9.3 ± 0.5 and 10.9 ± 0.6 m/s, respectively). In contrast, PWV for WCH in subgroup A (9.3 ± 0.5 m/s) did not differ ($P > 0.35$) from those for the normotensive subgroups A (9.2 ± 0.3 m/s) and B (9.6 ± 0.4 m/s). PWV was not correlated to levels of glycaemia, glycosylated haemoglobin and cholesterolaemia.

Conclusions These results suggest that, both for ambulatory hypertensives and for WCH, diabetes and dyslipidaemia are associated with an impairment of arterial distensibility that can entail a greater than normal cardiovascular risk, which might dictate a more than usually stringent treatment of concomitant risk factors and possibly of high blood pressure. In contrast, PWV in WCH of the subgroup A did not differ from those in normotensives, reinforcing the hypothesis that WCH is

associated with a benign cardiovascular outcome in the absence of other cardiovascular risk factors. *Blood Press Monit* 5:11–17 © 2000 Lippincott Williams & Wilkins.

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Introduction

Arterial hypertension is a disorder characterized early in its course by damage to vessels and heart [1,2]. The risk of cardiovascular disease in patients with hypertension is determined not only by the level of blood pressure but also by the presence or absence of other cardiovascular risk factors such as smoking, dyslipidaemia and diabetes [3–6]. It has been recognized not only that hypertension accelerates development of vascular complications of diabetes [7] but also that, for the same high level of blood pressure, the concomitance of other risk factors is associated with a greater risk of cardiovascular damage and a worse outcome [3–5,8]. Because of this, it has been recommended that diabetic patients and subjects with more than two cardiovascular risk factors with high blood pressures should be treated early and stringently [9]. White-coat hypertension (WCH) has been defined as a condition of a persistently high clinic blood pressure together with a normal ambulatory blood pressure [10]. The prognostic significance of WCH is still not completely known, but recent data suggest that it is a condition associated with low cardiovascular morbidity, for which treatment is not generally thought necessary [11]. Authors of several cross-sectional and prognostic studies have shown that hypertensive target-organ damage and abnormality of metabolic profile in subjects

with WCH are less than those in subjects with higher levels of ambulatory blood pressure [12–15] and these effects have been found similar in some studies [12–15] but not in all [16–18] to those of clinically normotensive subjects. Although it has been suggested that WCH is a pre-hypertensive state [19], it was recently found that subjects with WCH without any other major cardiovascular risk factors exhibited a tendency towards development of sustained hypertension that was similar to that of a normotensive control population [20]. Thus, it is possible that, in WCH, just like in sustained hypertension, the presence or absence of other cardiovascular risk factors dictates different degrees of the severity of cardiovascular target-organ damage, thereby discriminating groups for which treatment options may be differently justified. Arterial stiffness is now being recognized as an important independent risk factor for cardiovascular disease [21]. Pulse-wave velocity (PWV) has been used widely as an index of arterial distensibility and stiffness [22] that can now be measured automatically by recently validated devices [23]. Since large-artery damage is a major factor contributing to the worsening of cardiovascular prognosis, it is conceivable that a decrease in aortic distensibility reflects the damage to the arterial wall caused by various cardiovascular risk factors including hypertension. The aim of the present study was to determine, using a cross-sectional approach, whether aortic distensibility measured in terms of carotid-femoral PWV in normotensive subjects and in patients with WCH and sustained hypertension differs according to the presence or absence of other cardiovascular risk factors.

Methods

Study population

Patients with either sustained hypertension or WCH were selected from individuals referred to our unit for evaluation by ambulatory blood pressure monitoring and for the assessment of hypertension and overall cardiovascular risk. All of these had remained untreated with antihypertensive drugs for at least the previous 3 months. Normotensive controls were recruited from individuals working in the hospital. Only subjects aged 25–60 years, with normal renal function and body mass indices $< 27 \text{ kg/m}^2$ were used in the study. Subjects with previous histories of coronary heart disease, heart failure, cerebrovascular events, insulin-dependent diabetes and peripheral artery disease were excluded. Normotensives were all subjects with average clinic blood pressures $< 140 \text{ mmHg}$ systolic and $< 90 \text{ mmHg}$ diastolic and with mean awake ambulatory blood pressures less than 130 mmHg systolic and 85 mmHg diastolic. Subjects with WCH had average clinic blood pressures

$\geq 140 \text{ mmHg}$ systolic and $\geq 90 \text{ mmHg}$ diastolic and mean awake ambulatory blood pressures less than 130 mmHg systolic and 85 mmHg diastolic. Sustained hypertensive patients had average clinic blood pressures between 140 and 180 mmHg systolic and between 90 and 109 mmHg diastolic and mean awake ambulatory blood pressures $\geq 130 \text{ mmHg}$ systolic or $\geq 85 \text{ mmHg}$ diastolic, or both. All subjects classified as normotensives, white-coat hypertensives and sustained hypertensives were divided into two groups A and B. Group B included subjects with type-II diabetes according to established criteria [24] or with both smoking and hypercholesterolaemia (total cholesterol level $> 200 \text{ mg/dl}$); group A included subjects without diabetes and with only one or none of the two risk factors, smoking and dyslipidaemia.

Evaluation of blood pressure

Recordings of clinic systolic and diastolic blood pressures were performed in triplicate at 2-week intervals on the same arm, with the subject supine after 10 min of quiet rest, using an automatic sphygmomanometer. The average of the two readings was considered the measurement of that visit.

Ambulatory blood pressure monitoring was carried out for 25–26 h on a working weekday with a SpaceLabs 90207 monitor (SpaceLabs Inc., Redmond, Washington, USA). A Sentinel-pro interface (Rainbow Technologies, Inc, Irvine, California, USA) installed in an IBM/AT computer read and edited data. Ambulatory blood pressure measurements were validated by use of a Y-tube connection to a mercury manometer. The data were discarded if there was a difference greater than 5 mmHg between results obtained by using these two techniques. Blood pressure readings were obtained automatically at 20 min intervals while the subjects were awake (daytime) and asleep (night-time). Recordings were accepted only if more than 85% of the raw data were valid.

Automatic measurements of PWV

For automatic measurements of PWV, we used the automatic device Complior (COLSOM, Garges les Gonesse, France). Briefly, the pressure waveforms were digitized at 500 Hz acquisition frequency for carotid-femoral artery PWV. The two pressure waveforms were stored in a memory buffer. The delay between the two pulse waves was calculated by performing a correlation between the data of the two waveforms. The procedure was performed for 10 different cardiac cycles and their mean value was considered for analysis. Validation of this method by comparison with the standard method has previously been described [23].

Echocardiography

Echocardiographic examinations were performed at the time of the first visit. All subjects studied had suitable acoustic windows. The Doppler-echocardiographic data were recorded and read by the same trained observers, who were not aware of the blood pressures of the subjects examined, using a commercially available instrument (ALOKA SSD870 colour; Mitaka, Tokyo, Japan) equipped with a 3.5 MHz electronic transducer. Complete standard M-mode and two-dimensional echocardiographic data were recorded for all subjects. Left ventricular internal diameters [left ventricular end-systolic (LVSD), left ventricular end-diastolic (LVDD) and left atrium] and wall thicknesses [inter-ventricular septum thickness (IVST) and posterior wall thickness (PWT)] were obtained from the long-axis parasternal view as described previously [25,26]. Left-ventricle mass was calculated as described before [26] and indexed relative to body surface area [left ventricular mass index (LVMI)]. Left-ventricle shortening fraction (LVSF) [LVSF = (LVDD - LVSD)/LVDD] was also calculated. Recordings were analysed on-line from stop frames at an equivalent of 100 mm/s paper speed by means of commercially available software included in the instrument and stored on videotape (super-video home system) for further analysis.

Biochemical analysis

Venous blood samples were collected after a fasting period of 12 h for determination of levels of total serum cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, glycosylated haemoglobin and creatinine.

Statistical analysis

Data are expressed as means \pm SEM. Groups were compared with one-way analysis of variance and multiple comparisons (Tukey's test) and then by use of an unpaired Student's *t* test. The relationship between variables was evaluated by linear regression. For analysis of data from ambulatory blood pressure monitoring we used dedicated software developed in our department [27]. Frequency distribution was analysed with Fisher's exact test where appropriate in two-tailed tests, $P < 0.05$ was considered statistically significant.

Results

In Table 1 we show the characteristics of the populations studied, at the time of the examination. Because of the selection criteria, all groups and subgroups were similar in age, sex distribution and body mass index. Mean levels of serum lipids, glucose and glycosylated haemoglobin for subgroups A of normotensives, white-coat hypertensives and sustained hypertensives were similar. Hypertensive patients of the subgroup B had slightly but significantly greater levels of serum glucose and glycosylated haemoglobin than did normotensives and white-coat hypertensives of the subgroup B, whereas other biochemical parameters did not differ among the three subgroups B. Only subjects in subgroups B had diabetes, as a consequence of the entry criteria. Mean LVMI of the normotensives and of the white-coat hypertensives of the subgroups A and B were not statistically different; LVMI of the patients with sustained hypertension (of both subgroups A and B) were significantly greater than those of subgroups A

Table 1 Clinical laboratory data and blood pressures for normotensive, white-coat-hypertensive (WCH) and sustained-hypertensive subjects

	Normotensive group A	Normotensive group B	WCH group A	WCH group B	Ambulatory hypertension group A	Ambulatory hypertension group B
	(n=19)	(n=16)	(n=28)	(n=18)	(n=37)	(n=44)
Age (years)	42 \pm 4	44 \pm 3	44 \pm 5	45 \pm 6	46 \pm 5	47 \pm 3
Sex (male/female)	9/10	8/8	13/15	8/10	12/15	19/25
BMI (kg/m ²)	23.2 \pm 0.3	23.9 \pm 0.4	23.8 \pm 0.5	24.2 \pm 0.6	24.6 \pm 0.6	25.4 \pm 0.5*
Clinic blood pressure (mmHg)	125 \pm 4/82 \pm 2	126 \pm 3/82 \pm 2	148 \pm 5/91 \pm 3 [†]	150 \pm 4/94 \pm 2 [†]	157 \pm 3/99 \pm 4 [†]	160 \pm 3/98 \pm 2 [†]
Daytime blood pressure (mmHg)	123 \pm 2/79 \pm 2	124 \pm 2/80 \pm 2	125 \pm 5/81 \pm 3	127 \pm 2/82 \pm 2 [†]	150 \pm 6/98 \pm 4 [†]	146 \pm 3/95 \pm 2 [†]
Night-time blood pressure (mmHg)	104 \pm 2/68 \pm 1	107 \pm 2/72 \pm 2	106 \pm 2/72 \pm 2	110 \pm 2/75 \pm 3* [†]	130 \pm 4/86 \pm 3 [†]	131 \pm 5/88 \pm 3 [†]
Smoking	4	7	8	9	9	11
Diabetes of type 2	0	11	0	12	0	32
Dyslipidaemia	5	13	9	10	16	28
Glycaemia (mg/dl)	86 \pm 2	142 \pm 12*	89 \pm 3	151 \pm 14*	95 \pm 9	162 \pm 22*
HbA1-C (mg/dl)	4.9 \pm 0.2	8.6 \pm 1.4*	5.3 \pm 0.4	9.4 \pm 1.7*	5.9 \pm 0.6	9.8 \pm 2.0*
Total cholesterol (mg/dl)	172 \pm 6	236 \pm 16*	179 \pm 8	248 \pm 19*	184 \pm 10	258 \pm 22*
HDL cholesterol (mg/dl)	41 \pm 1	39 \pm 2	41 \pm 2	39 \pm 2	38 \pm 3	38 \pm 4
Triglycerides (mg/dl)	103 \pm 4	128 \pm 8*	107 \pm 5	139 \pm 12*	114 \pm 9	156 \pm 19*
Creatinine (mg/dl)	0.8 \pm 0.1	0.8 \pm 0.1	0.9 \pm 0.1	0.9 \pm 0.2	0.9 \pm 0.2	1.0 \pm 0.3
LVMI (g/m ²)	90 \pm 2 [12]	93 \pm 3 [11]	92 \pm 2 [20]	95 \pm 2 [17]	103 \pm 3 [31] [†]	108 \pm 4 [39]*

Values are expressed as means \pm SEM [numbers of subjects]. Subgroups B include subjects with some combination of diabetes, dyslipidaemia and smoking; subgroups A include non-diabetic subjects without cardiovascular risk factors or with only either smoking or dyslipidaemia. HbA1-C, glycosylated haemoglobin; LVMI, left ventricular mass index. BMI, body mass index; HDL, high-density lipoprotein. * $P < 0.05$, versus subgroup A; [†] $P < 0.05$, versus normotensive groups A and B.

and B of the populations of normotensives and white-coat hypertensives. Carotid-femoral PWV for the normotensive population (both subgroups A and B) and for the subgroup A of the population of white-coat hypertensives were not significantly different (Fig. 1). In comparison with these three groups, significantly greater carotid-femoral PWV (i.e. lower aortic distensibilities) were observed for the subgroup B of white-coat hypertensives and the two subgroups (A and B) of the sustained-hypertensive population. Also for the subgroup B of the sustained hypertensive population we found significantly greater PWV than we did both for the subgroup A of sustained hypertensives and for the subgroup B of the white-coat hypertensive subjects.

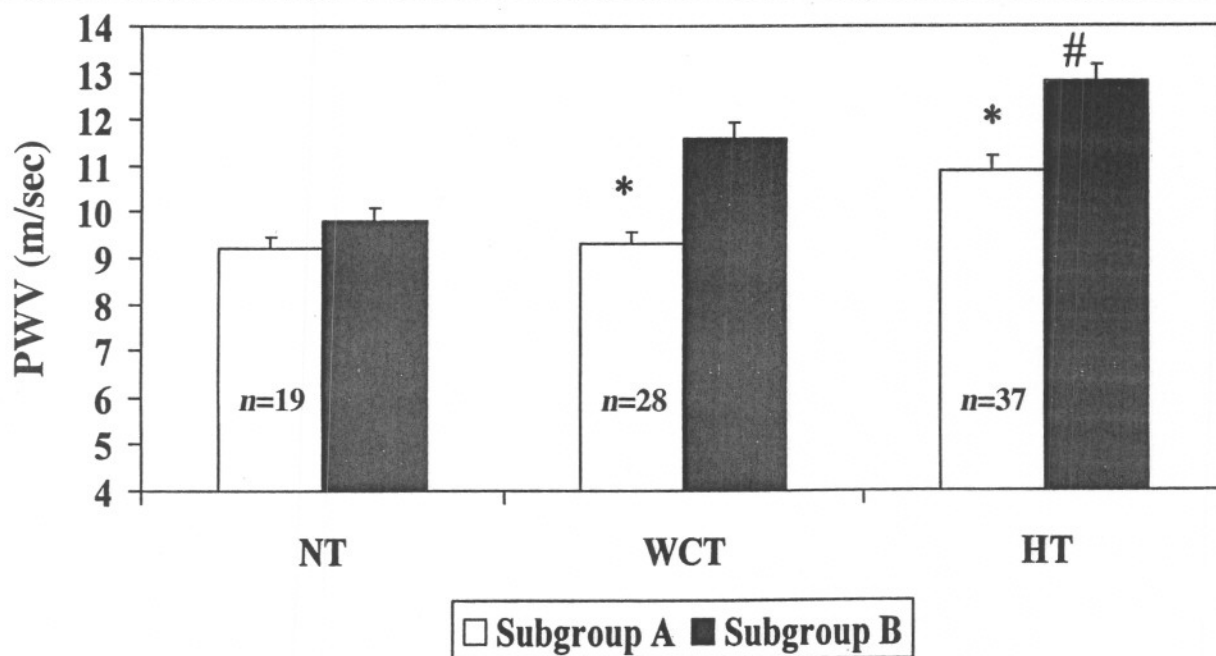
We found significant correlations between LVMI (which was evaluated for 130 of the 162 subjects studied) and daytime systolic and diastolic blood pressures ($r = 0.482$, $P < 0.01$ and $r = 0.419$, respectively) but not clinic blood pressures and between PWV (for all 162 subjects) and daytime systolic ($r = 0.525$, $P < 0.01$) and diastolic ($r = 0.418$, $P < 0.01$) blood pressure. Considering all subjects of the subgroups B ($n = 84$), the correlation coefficient for relationship between PWV and systolic blood pressure was $r = 0.624$ ($P < 0.001$), whereas for the subjects ($n = 78$) of the subgroups A it was $r = 0.492$ ($P < 0.01$). We observed no significant correlation between LVMI or PWV and the levels of glycaemia, glycosylated

haemoglobin, total cholesterol, high-density lipoprotein cholesterol and triglycerides.

Discussion

A decrease in arterial distensibility of the large arteries (i.e. an increase in arterial stiffness) not only increases the workload on the heart but also has been identified as an important independent risk factor for cardiovascular disease [21,28]. The increase of arterial stiffness has been found to be related to several cardiovascular risk factors such as age [23], hypertension [23,29], diabetes mellitus [30] and hyperlipidaemia [31] and to be associated with a common denominator of cardiovascular disorders, namely endothelial dysfunction [32]. Also, because stiffening of arteries might raise systolic blood pressure, which is an independent predictor of cardiovascular morbidity, it has been postulated that stiffness of the arterial tree plays a role in the pathogenesis of cardiovascular diseases including atherosclerosis [28]. Moreover, it has been suggested [28] that the measurement of arterial stiffness is useful for stratification of cardiovascular risk and targetting of treatment. Well-validated and reproducible techniques for obtaining non-invasive measurements of aortic distensibility in the clinical setting by the determination of carotid-femoral PWV have recently been developed [23].

Fig. 1



Carotid-femoral pulse-wave velocities (PWV), in normotensive (NT), white-coat-hypertensive (WCH) and sustained-hypertensive (HT) subjects. Subgroups B include subjects with some combination of diabetes, dyslipidaemia and smoking; subgroups A include non-diabetic subjects without cardiovascular risk factors or with only either smoking or dyslipidaemia. * $P < 0.04$, versus subgroup B; # $P < 0.04$, versus all other groups.

In the present study we estimated and compared the aortic distensibilities, measured in terms of carotid-femoral PWV, of groups of normotensive, white-coat-hypertensive and sustained-hypertensive subjects matched for body mass index and age, who were subdivided according to the criteria of presence versus absence of major cardiovascular risk factors. As reported by others [23,33], in this study aortic PWV was correlated well to daytime ambulatory systolic blood pressure but not to levels of glycaemia and total plasma cholesterol. Although some authors have suggested that the increase in PWV could be an early marker of atherosclerosis [34], it is not surprising that PWV is correlated strongly to systolic blood pressure since one of the major factors influencing systolic blood pressure is arterial distensibility [35]. However, the most striking finding of the present study was that aortic PWV as an indicator of aortic distensibility did discriminate white-coat hypertensives with several cardiovascular risk factors from the ones without. We found a striking difference between PWV of white-coat-hypertensive subjects with and without more than one major cardiovascular risk factors, indicating that, particularly in that group, the presence of diabetes with or without other cardiovascular risk factors was associated with a markedly lower than normal aortic distensibility. It is plausible that the high prevalence of diabetes of type 2 in subgroups B is the principal cause of PWV in members of these subgroups being higher, since it is well recognized that arterial rigidity is strongly related to diabetes [30]. What was intriguing in our study was that, differently from PWV in subjects with white-coat hypertension and sustained hypertensives, PWV in the normotensive subjects did not differ between subgroups A and B, although there was a tendency for PWV in members of the subgroup B to be higher. It is possible that the small sample for the normotensive group explains why statistical significance was not obtained when these subgroups were compared. Also the tendency for PWV in members of subgroup B of white-coat hypertensives to be greater than PWV in members of the subgroup B of normotensives could have several possible explanations. It is plausible that the slightly greater (by 2–3 mmHg) average ambulatory blood pressure in members of subgroup B of white-coat hypertensives than in members of subgroup B of normotensives together with slightly greater plasma levels of glucose, cholesterol and triglycerides were important enough to produce slightly greater PWV in members of the former group.

Nowadays there is a continuing debate about whether WCH is an innocent state or whether it is associated with greater than normal global cardiovascular risk. Although authors of several studies [12–15] found no evidence that there is structural and functional organ

damage in, or a greater than normal incidence of cardiovascular events among, subjects with WCH, others [16–18] have reported that this condition is characterized by a greater than normal left ventricular mass, alteration of cardiac function and renal dysfunction. The basis for all these discrepancies might lie not only in use of different definitions of WCH and differences among demographic characteristics of the populations but also in differences related to the concomitant presence or absence of other cardiovascular risk factors. It has been suggested by authors of a recent 2–5-year-follow-up study [20] that subjects with WCH without any other major cardiovascular risk factors exhibit a similar propensity towards development of sustained hypertension to that of normotensives in a clinic. We showed in the present study that the greatest difference between PWV for the subgroups A and B occurred within the white-coat-hypertensive population, although PWV in members of the subgroup B of sustained-hypertensive subjects was also higher than that for the subgroup A and, even in the normotensive group, there was also a tendency for PWV in members of subgroup B to exceed that in members of subgroup A. Considering all six subgroups that were examined in this study, although we found similar ranking orders for LVMI and aortic PWV, differently from what was observed with PWV, the differences between LVMI for subgroups A and B of the white-coat hypertensives did not attain statistical significance. The correlation between PWV and systolic blood pressure appeared to be stronger for the population with some combination of diabetes, smoking and high total cholesterol levels than it was for the population with one or no risk factor. Since neither PWV and glycaemia nor PWV and total plasma cholesterol levels were correlated, we may speculate that, when diabetes or other cardiovascular risk factors are present, these conditions may either contribute by increasing damage of the artery wall or amplify the impact of blood pressure on the arterial stiffness. It is well known that most cardiovascular risk factors are associated with the occurrence of endothelial dysfunction, which causes an imbalance between production of relaxing and antiproliferative substances such as NO and production of vasoconstrictors and pro-proliferative factors such as endothelin [36]. Endothelial dysfunction has been associated with greater than normal arterial stiffness [32]. It is plausible that, within the threshold of variation of blood pressure observed in subjects with WCH, the presence of other cardiovascular risk factors works as a crucial trigger for the expression of the damage to target organs such as large arteries. Recently published guidelines [9,37] have established that decisions about the management of patients with high blood pressures should be based not on the level of blood pressure alone but also on the

presence of other risk factors and concomitant diseases. In fact, it is now assumed that the higher the baseline risk the greater the benefit to be gained from treatment. The present results reinforce this view, particularly insofar as the management of subjects with WCH is concerned. We conclude that, just like for sustained hypertensive patients, among white-coat hypertensives the concomitant presence of diabetes, dyslipidaemia, or both, is associated with an impairment of arterial distensibility that can entail an increase in cardiovascular risk. Although this conclusion is speculative, it could be a further argument for more stringent application of anti-hypertensive therapy to the white-coat-hypertensive subjects with other risk factors. However, even for patients in these groups the potential benefits of more stringent treatment of the concomitant risk factors (smoking, high level of cholesterol and diabetes) may be greater than that of any antihypertensive treatment. In that context, any decision on initiating antihypertensive therapy must take into account first that antihypertensive medication does not seem to be able to lower an awake ambulatory blood pressure below 130/85 mmHg [38] and second that administration of some antihypertensive drugs can even result in a worsening of lipidaemia and control of diabetes. Meanwhile, in our study we clearly showed that arterial distensibility in white-coat hypertensives with one or no risk factor, measured in terms of PWV, was no different from that of clinically normotensive subjects. This reinforces the hypothesis that WCH is associated with a benign cardiovascular outcome in the absence of other cardiovascular risk factors for which antihypertensive therapy is generally not indicated.

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