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Target Organ Damage and Changes in Arterial Compliance in White Coat Hypertension. Is White Coat Innocent?

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The aim of this study was to perform an extensive evaluation of target organ status, metabolic abnormalities and hemodynamic alterations in white coat hypertension (WCH). Fifty normotensive (NT), 90 WCH (ambulatory daytime blood pressure <135/85 mmHg) and 101 hypertensive (HT) subjects underwent extensive biochemical, echocardiographic, fundoscopic examination. In a subgroup study, arterial compliance and intima-media thickness (IMT) were measured by Doppler ultrasound in left common carotid artery. WCH subjects were found to have higher body mass index (BMI) than the NTs ($p = 0.042$). Left ventricle mass index (LVMI) was greater in the WCHs than the NTs ($p < 0.001$), but significantly less than the HTs ($p < 0.001$). Hypertensive retinopathy was observed in the WCHs, but was less severe and rare compared to the HTs (13% vs 27 %). Both WCHs and HTs had high levels of urinary albumin excretion (UAE) (p = not significant). Total cholesterol was higher in WCHs than in the NTs ($p = 0.04$) The distensibility coefficient (DC) of the WCHs was significantly greater than the HTs ($p < 0.01$), while significantly smaller than the NTs ($p < 0.01$). The compliance coefficient (CC) of the WCHs was significantly higher than the HTs ($p < 0.01$), and significantly less than the NTs ($p < 0.01$). The IMT in the HTs was significantly higher than the WCHs (0.81 ± 0.05 vs 0.70 ± 0.04 mm; $p < 0.001$) and the NTs ($p < 0.001$). The difference between the NTs and the WCHs was not significant. Our data indicate that patients with WCH represent an intermediate group between NTs and sustained HTs where target organ damage and cardiovascular risk is concerned. *Key words: arterial compliance, left ventricular mass index, white coat hypertension.*

INTRODUCTION

White coat hypertension (WCH) is generally defined as a persistently elevated clinic blood pressure in combination with a normal ambulatory blood pressure (ABP). There is disagreement regarding the optimal cut-off point for ABP. The white coat effect is defined as the difference between the clinic blood pressure and daytime ABP [1]. Subjects with WCH are characterized by elevated arterial pressures in the physician's office, but 'normal' pressures at other times. The prevalence of WCH varies according to the definition of WCH and the population studied, but is reported to be approximately 20% [1]. The prognosis for WCH is not yet completely clear. Several studies indicated a good prognosis of this condition by demonstrating a low-degree end organ damage [2–4]. Other authors reported that WCHs exhibit end-organ damage [5–6] and metabolic abnormalities such as hyperlipidemia, impaired insulin sensitivity, elevated blood glucose and increased serum insulin levels [7–9]. The aim of this study was to perform an extensive evaluation of target organ status, metabolic abnormalities and hemodynamic alterations in WCH.

MATERIALS AND METHODS:

The study population consisted of 90 WCH (20 males, 70 females) and 101 hypertensive (HT; 49 males, 52 females) subjects referred to our outpatient hypertension unit between June 2001 and December 2002, and 50 normotensive (NT; 21 males, 29 females; clinical diastolic pressure <90 mmHg) controls. Brachial arterial pressures were obtained by a nurse with a mercury sphygmomanometer, which was standardized in accordance with the approval of American and British Hypertension Society and World Health Organisation. Measurements were obtained in the sitting position after resting for 20–30 min [10–12]. Korotkoff phase I was used to determine the systolic blood pressure and phase V was used for diastolic blood pressure. Measurements were

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performed on three different occasions within 5 days. The average of three measurements was taken as systolic and diastolic blood pressures.

An ambulatory 24-h arterial blood pressure monitoring (ABPM) was performed in patients with diastolic pressure >90 mmHg in the outpatient department, with the ABPM device instrument (A and D Engineering, TM-2421) approved by the European Hypertension Society [13]. Measurements were performed on the left arm as suggested by the British Hypertension Society [14]. Patients were classified into sustained (clinical diastolic pressure >90 mmHg and ambulatory daytime diastolic pressure >85 mmHg) or WCH (clinical diastolic pressure >90 mmHg and ambulatory daytime arterial pressure <135/85 mmHg) groups according to the results of the ambulatory measurement.

All patients underwent standard echocardiographic examination, fundoscopy, blood and urine analysis.

Echocardiography

Indexes of cardiac structure and function were assessed at baseline only. Left ventricular end-diastolic posterior wall thickness, interventricular septal wall thickness at end diastole, left ventricular internal end diastolic diameter (LVIDD) and left ventricular internal end-systolic diameter (LVIDS) were measured using the American Society of Echocardiography convention from M-mode images of the left ventricle, generated in the short axis view at the level of the mitral chordea (2.5 MHz; Hewlett Packard 2500) Using these measurements, left ventricular mass (LVM), and left ventricle mass index were (LVMI) calculated [15–16].

Biochemical analysis

Serum total cholesterol (TC), high-density lipoprotein (HDL), triglyceride (TG), low-density lipoprotein (LDL), glucose, urea, creatinin and 24-h creatinin clearance were measured using standard enzymatic methods using a fully automated analyzer (Olympus AU-800). Blood samples were taken from the antecubital vein after an overnight fast. Microalbuminuria in 24 h was measured with radioimmunoassay (RIA). Urinary albumin excretion (UAE) between 30 and 300 mg/day were taken as microalbuminuria.

Fundoscopic classification of hypertensive retinopathy (HTRP) was done by an experienced ophthalmologist according to Keith, Wagener & Barker classification [17]. In the *subgroup analysis* to assess the hemodynamic alterations patients with hyperlipidemia (LDL >130 mg), any signs or symptoms of atherosclerotic vascular disease, diabetes mellitus and other endocrine diseases, obesity (body mass index, BMI > 27), drugs that may affect blood pressure and lipid metabolism, smoking and alcoholism were excluded, so that 24 WCHs (group I; 11 males, 13 females), 21 HTs (group II; 10 males, 11 females) and 21 NTs (group III; 10 males, 11 females) underwent Doppler ultrasonographic examination.

Ultrasonogrophic examinations were performed in a quiet, temperature-controlled room (22°C) after overnight fasting. After 20 min rest, the examinations were done between 08.30 and 10.00 h with a color Doppler ultrasound unit (Siemens Elegra, Erlangen, Germany) equipped with a 7.5-l, 40-MHz transducer. Patients were examined in a supine position. All ultrasonographic measurements were performed with an experienced radiologist blinded to grouping of the patients. B-mode ultrasound scans of the left (L) common carotid arteries were performed. The lumen diameter of the common carotid artery, 1 cm proximal to the bulb, was measured as the distance between intima–blood interface anteriorly and intima-blood interface posteriorly. All measurements were made at the time of scanning on frozen images of longitudinal scans by using the machine's electronic caliper. Using the cine-mode of the machine, systolic and diastolic lumen diameters were taken separately, and the differences between them were calculated. The difference between the anterior and posterior wall represents arterial distension, i.e. change in diameter during one heart cycle. Data for arterial diastolic diameter (D) and distention (ΔD) were obtained for each heartbeat. Brachial blood pressure was measured with a semiautomatic oscillometric device (Dinamap). Pulse pressure was defined as systolic minus diastolic pressure (ΔP). Vessel wall properties were calculated according to the following equations:

$$\text{Distensibility coefficient (DC)} = (2\Delta D/D)/\Delta P(\text{in } 10^{-3}/\text{kPa})$$

$$\text{Compliance coefficient (CC)} = TTD\Delta D/2\Delta P(\text{in mm}^2/\text{kP}^{-1}a) \quad [18]$$

Each measurement was repeated three times on occasion and the mean value for each measurement was calculated. The measurements of 10 different patients were obtained twice with a 2-h interval and RC (repeatability coefficient) values were 0.35 mm for systolic diameter and 0.18 mm for diastolic diameter, which were not statistically different from zero [19].

Statistical analysis

Data are expressed as mean ± SD. Groups were compared with ANOVA Tukey HSD. Frequency distribution of HTRP was analyzed with Pearson χ^2.

Table I. *The characteristics of the groups*

	NT (I), $n = 50$	[a]p	WCH (II), $n = 90$	[b]p	HT (III), $n = 101$	[c]p
Age	46 ± 11		$50 \pm 11\pm$		48 ± 11	
Gender (M/F)	21/29		20/70		49/52	
BMI (kg/m^2)	25.8 ± 4	0.045	29.0 ± 4		27.9 ± 4	

NT, normotensives; WCH, white coat hypertensives; HT, hypertensives. [a]p, difference of NT from WCH; [b]p, difference of WCH from HT; [c]p, difference of HT from NT.

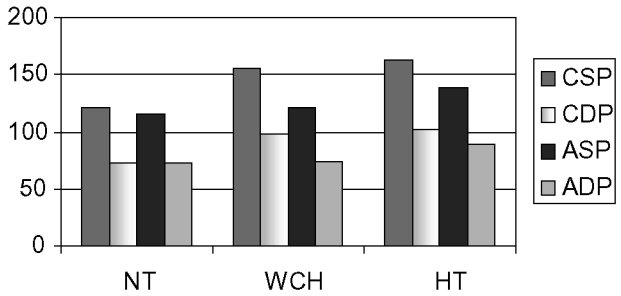

Fig. 1. The clinical and daytime ambulatory blood pressure values of the groups. NT, normotensives; WCH, white coat hypertensives; HT, hypertensives; CSP, clinical systolic pressure; CDP, clinical diastolic pressure; ASP, ambulatory systolic pressure; ADP, ambulatory diastolic pressure. Both clinical systolic and clinical diastolic pressures of WCH and HT groups are significantly different from the NT group ($p < 0.001$). Both ambulatory systolic and ambulatory diastolic pressures of WCH group are significantly different from the HT group ($p < 0.001$).

RESULTS

The characteristics of the study population are given in Table I. The age and gender distribution of the groups were similar. BMI was higher in the WCH group, but the difference was significant only when compared to NTs (29.0 ± 4 vs 25.8 ± 4; $p = 0.045$).

Figure 1 shows clinical and ambulatory blood pressure (ABP) values in NT, WCH and HT groups. In clinical measurements, systolic pressures were 121 ± 11, 156 ± 21 and 163 ± 24 mmHg and diastolic values were73 ± 8, 98 ± 11 and 102 ± 10 mmHg, respectively. Both systolic and diastolic pressures of WCH and HT groups were significantly different from the NT group ($p < 0.001$). In ambulatory daytime measurements, systolic pressures were 116 ± 6, 121 ± 6 and 139 ± 11 mmHg and diastolic pressures were 73 ± 3, 74 ± 5 and 89 ± 8 mmHg, respectively. Both systolic and diastolic pressures of WCH group were significantly different from the HT group ($p < 0.001$).

Table II summarizes the laboratory data. Total cholesterol was significantly higher in the WCH group than in the NTs (220 ± 43 vs 190 ± 44 mg/dl, $p = 0.04$). It was also significantly higher in the HT group than in the NTs (222 ± 43 mg/dl; $p = 0.03$). There was no significant difference between the HT and the WCH groups. Triglyceride levels were significantly greater in the HT than NT group (165 ± 100 vs 102 ± 53 mg/dl; $p = 0.04$). The difference between HT and WCH was not significant (165 ± 100 vs 143 ± 60 mg/dl; $p = 0.29$). Both WCH and HT groups had high levels of UAE (35.8 ± 8.1 and 35.8 ± 9 mg/day, respectively), but the differences between the groups were not significant. Other laboratory parameters (glucose, urea, creatinin, creatinin clearance, uric acid) were similar among the three groups.

Table II. *The biochemical characteristics of the study groups*

	NT (I), $n = 50$	[a]p	WCH (II), $n = 90$	[b]p	HT (III), $n = 101$	[c]p
TC, mg/dl	190 ± 44	0.04	220 ± 43		222 ± 43	0.03
Triglyceride, mg/dl	102 ± 53		143 ± 60		165 ± 100	0.04
HDL-C, mg/dl	48 ± 9		47 ± 21		44 ± 18	
LDL-C, mg/dl	121 ± 41		143 ± 41		145 ± 38	
VLDL-C, mg/dl	20 ± 14		30 ± 15		31 ± 20	
Glucose, mg/dl	96 ± 3		101 ± 15		103 ± 27	
Urea, mg/dl	29 ± 7		28 ± 8		31 ± 8	
Creatinin, mg/dl	0.77 ± 0.1		1.12 ± 2		0.77 ± 0.1	
GFR, mg/min	72 ± 12		85 ± 33		84 ± 29	
UAE, mg/day	29.8 ± 6.2		35.8 ± 8.1		35.8 ± 9	

NT, normotensives; WCH, white coat hypertensives; HT, hypertensives; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; GFR, glomerular filtration rate; UAE, urinary albumin excretion. [a]p, difference of NT from WCH; [b]p, difference of WCH from HT; [c]p, difference of HT from NT.

Table III. *The ratio of hypertensive retinopathy in groups*

Hypertensive retinopathy	Normotensive (I), $n = 50$	WCH (II), $n = 90$	Hypertensive (III), $n = 101$	Total, $n = 241$
Stage I	0	9 (10%)	14 (14%)	23 (9%)
Stage II	0	3 (3%)	12 (12%)	15 (6%)
Stage III	0	0	1 (1%)	1 (0.4%)
Total	0	12 (13%)	27 (27%)	39 (16%)

LVMI was greater in WCH group compared to the NTs (94 ± 21 vs 81 ± 13 g/m^2; $p = 0.001$), but significantly less than HTs (103 ± 24 g/m^2; $p = 0.005$).

HTRP was observed in WCH, but was less severe and rare compared to HTs (13% vs 27 %) (Table III).

Characteristics of the subgroups are given in Table IV. Mean age, gender distribution and BMI did not differ among the three subgroups.

Table V shows the IMT and functional vessel wall properties in the subgroups. The IMT in the HT group was significantly higher than in the WCH and the NT groups (0.81 ± 0.05, 0.70 ± 0.04 and 0.68 ± 0.04 mm respectively; $p < 0.001$). Despite having a higher value, the WCH group did not differ from the NT group significantly. The DC of the WCH group was significantly greater than that of the HTs (17.18 ± 2.36 vs 10.18 ± 2.9610^{-3}/kPas; $p < 0.001$), but significantly smaller than that of the NTs (21.85 ± 2.22; $p < 0.001$). The CC of the WCH group was significantly higher than that of the HTs (0.60 ± 0.03 vs 0.42 ± 0.03 mm^2/kPas; $p < 0.01$), and significantly lower than that of the NTs (0.77 ± 0.03; $p < 0.01$).

DISCUSSION

Existing data on the prognostic and clinical significance of WCH is controversial. It is considered to be a clinical situation by some authors, whereas others have found an increased risk for cardiovascular diseases [1]. The major factor in these discrepancies is the disagreement regarding the optimal cut-off point for ABP. There also exist data indicating that the clinic-daytime average blood pressure difference does not reflect the alerting reaction and the pressure response elicited by the physician's visit and thus is not a reliable measure of the white coat effect [20]. The recently published (after the completion of this study) 'Guidelines for Management of Hypertension' defines WCH as office blood pressure $\geq$140/90 mmHg (at several visits) and 24 h ABP $<$125/80 mmHg [21]. Although we use a higher cut-off value (135/85 mmHg), the mean values for ambulatory systolic and diastolic pressures of the WCH group are within recently accepted limits so that the new definition would not alter the results significantly.

Cardillo [22], Kuwajima [23], Liu Je [24] and Weber [25] reported an increased LVMI in patients with WCH compared to normotensives. Our findings are consistent with these data. LVMI of the WCH group is significantly less than that of HTs and significantly greater than that of NTs, indicating an intermediate risk group where cardiac damage is concerned. Contrary to these findings, White & Hoeghelm reported that WCHs and NTs have similar LVMI values [26–27]. It should be emphasized that in White's study, 130/80 mmHg was taken as the cut-off point for WCH. Compared to our study, the patients between 135 and 130 in systolic and 85 and 80 in diastolic blood pressures were not enrolled. These pressure values are the degrees supposed to cause damage in the target organs. In Hoeghelm's study group [27], it was noticeable that 17% of WCH group had higher LVMI than the NT group. This may be the clue of impending cardiovascular risk and this ratio may increase with the disease duration. The duration of WCH, a factor not assessed/assessable in most of the studies is an important confounding factor in the development of target organ damage. The duration of the WCH and HT is thought to be one of the most

Table IV. *The characteristics and blood pressure values of subgroups*

	NT (I), $n = 26$	[a]p	WCH (II), $n = 24$	[b]p	HT (III), $n = 21$	[c]p
Age	48.9 ± 10		49.7 ± 11		47.2 ± 11	
Gender (M/F)	12/14		11/13		10/11	
BMI, kg/m^2	24.3 ± 5		25.3 ± 4		25.7 ± 6	
SBP, mmHg	128 ± 6		129 ± 5	<0.001	162 ± 7	<0.001
DBP, mmHg	81 ± 3		80 ± 2	<0.001	98 ± 2	<0.001

NT, normotensives; WCH, white coat hypertensives; HT, hypertensives; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table V. *The LVM, LVMI, IMT and functional vessel wall properties of the subgroups*

	NT (I), $n = 26$	[a]p	WCH (II), $n = 24$	[b]p	HT (III), $n = 21$	[c]p
LVM, (g)	135 ± 23	<0.001	168 ± 39	$=0.027$	190 ± 53	<0.001
LVMI, ($g/m^{2)}$	81 ± 13	<0.001	94 ± 21	$=0.005$	103 ± 24	<0.001
IMT, (mm)	0.68 ± 0.04		0.70 ± 0.04	<0.001	0.81 ± 0.05	<0.001
DC, 10^{-3}/kPa	21.85 ± 2.22	<0.001	17.18 ± 2.36	<0.001	10.18 ± 2.96	<0.001
CC, mm^2/ Pa	0.77 ± 0.03	<0.01	0.60 ± 0.03	<0.01	0.42 ± 0.03	<0.01

NT, normotensives; WCH, white coat hypertensives; HT, hypertensives; LVM, left ventricle mass; LVMI, left ventricle mass index; IMT, intima-media thickness; DC, distensibility coefficient; CC, compliance coefficient.
[a]p, difference of NT from WCH; [b]p, difference of WCH from HT; [c]p, difference of HT from NT.

important confounding factors in comparing their effects on target organs. A more recent, large-scale study, the PAMELA study, showed that in the patients with isolated office hypertension, LVMI was greater than in NT subjects, suggesting that it is not an entirely harmless phenomenon [28].

Where metabolic changes are concerned, our findings indicate that WCH have a similar profile to HTs with higher TC, LDL-C and TG values compared to NTs. Existing data obtained in different studies are controversial [25, 29–30]. Julius [30] suggested that WCH patients may be characterized by a lipid profile similar to that in sustained HT patients, which includes low HDL-C and high TG values that can increase high cardiovascular risk. Pierdomonico [29] reported that global lipid profile was similar in the WCH and NT subjects. Weber [25] was in agreement with Pierdomenico. We found no difference among the groups where blood glucose, urea, creatinin levels and glomerular filtration rate (GFR) are concerned. These discrepancies may depend on different populations studied, dietary and smoking habits, sample size and the exclusion criteria in different studies.

Kidney is one of the most frequently affected organs in sustained hypertension, and microalbuminuria has been shown to be positively correlated with blood pressure values in non-diabetic HT individuals [31–32] and may represent a marker of early hypertension-related target organ damage. Microalbuminuria had been associated with vascular disease and increased mortality in non-diabetic subjects [33–35]. In our study, UAE of WCH and HT patients were similar and higher than that of NTs. Pierdomenico [29] did not find microalbuminuria in either WCH or NT subjects. Hoegholm [36] showed that WCH subjects display less renal involvement than sustained HT subjects, even though they are characterized by slightly higher UAE values than NT subjects. We are in agreement with Hoegholm and think that UAE may increase with the duration of the disease.

In our study, none of the NT patients had fundoscopic changes, whereas 13% of the WCH and 27% of the HTs had retinal changes, another finding indicating WCH as an intermediate risk group for end organ damage.

The sub-study was designed to evaluate the changes in arterial compliance caused solely by WCH, so that patients with additional characteristics that may confound reduction in arterial compliance are excluded. Our findings indicate a reduction in arterial compliance both in the WCH and in the HT groups with decrease in DC and CC. WCH have significantly lower values than NTs but higher than HTs. Gomez [37] and Soma [35] arrived at the same results, but the differences between their WCH and HT groups were not significant. In Soma's study this may be due to different cut-off point for WCH because he enrolled the patients with the ambulatory daytime blood pressure less than 140/90 in the WCH group. The values of the arterial compliance may be closer to the HT group due to higher blood pressures of the patients included in the WCH group.

Carotid arterial intima-media thickness (IMT) is used to measure the progression of atherosclerosis [38]. In the current study, IMT was significantly greater in the HT group than the WCH and NT groups. Despite the greater values in the WCH group, the difference between the WCH and NT groups was not significant. Our findings on IMT were in agreement with Pierdomenico [29], Roman [39] and Gariepy [40]. There exists no study reporting significant difference between the WCH and NT. Rajdeep [41], after a 10-year follow-up study, found a lower incidence of left ventricular hypertrophy and lesser degrees of carotid hypertrophy in the WCH group. However, an important point to be noticed is that there was a significant difference between the WCH and HT groups concerning age (44 ± 12 vs 52 ± 10 years; $p < 0.001$). Since age is considered a risk factor for the developing of atherosclerotic endothelial dysfunction and structural changes, the differences between the groups may partly be due to the different ages. Silveria [42] measured carotid–femoral pulse wave velocity (PWV) as an index of aortic stiffness and LVMI in WCH subjects, and showed significantly lower PWV and LVMI than in HTs. Comparing to our findings, they took 130 mmHg as the cut-off point for the systolic pressure, and this difference of 5 mmHg may be the cause of the stiffness in the WCH group in our study. Another finding by

Rajdeep was that WCHs had a significantly lower incidence of cardiovascular events than sustained HTs had, and in his multivariate analysis, WCH was found to be an independent predictor of subsequent cardiovascular events. Other independent predictors were age, sex, race and smoking. These follow-up data support the findings indicating existence of cardiovascular and other end organ changes in WCH.

In summary, our data indicate that patients with WCH represent an intermediate group between NTs and sustained HTs where target organ damage and cardiovascular risk are concerned. The changes in end organs do exist, although not as severely as in HTs, and may become worse with the duration of WCH. The changes in end organs as a function of disease duration need to be investigated in long-term follow-up studies, but existing data indicate that WCH should not be considered a harmless trait.

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