White coat hypertension and haemostatic/fibrinolytic balance disorders

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Accepted for publication May 31, 2006

ABSTRACT. White coat hypertension (WCH) or isolated clinic hypertension is generally accepted to be a benign condition, although some reports have suggested that it may be associated with an increased cardiovascular event rate or other cardiovascular alterations. It has been previously shown that essential hypertension (EH) is associated with abnormalities in haemostatic/fibrinolytic balance and endothelial function. The aim of our study was to assess the impact of WCH on fibrinolytic balance and endothelial function by measuring plasma levels of plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator antigen (tPA), fibrinogen, and thrombomodulin. These markers were determined in 71 patients with EH, 26 with WCH and 87 normotensive healthy control subjects. The three groups were not different with respect to age, gender, smoking habits, BMI and blood lipids. Subjects with WCH were found to have increased plasma levels of PAI-1, tPA, fibrinogen and thrombomodulin compared to controls, but less compared to hypertensive ones. Our results suggest that WCH may be associated with decreased fibrinolytic potential and endothelial dysfunction, indicating that WCH may not be a completely harmless trait.

Keywords: white coat hypertension, haemostasis, fibrinolysis

White coat hypertension (WCH) or isolated clinic hypertension is defined as the observation of blood pressure (BP) levels greater or equal to 140/90 mmHg in several visits in the clinic, while 24-hour ambulatory blood pressure monitoring (ABPM) levels are found less than 125/80 mmHg [1, 2]. Among patients with clinic hypertension, the prevalence of WCH varies from 15% to 35%, depending on definitions [3]. Most previous studies have shown that patients with WCH are at substantially reduced risk of morbidity compared with patients whose hypertension is sustained throughout 24 hours, and this risk burden is not significantly different from normotensive ones [3-6]. However, other reports suggest that WCH is not entirely devoid of an increased cardiovascular event rate and may not be a completely benign condition [7-9]. Furthermore, different conclusions have been reached by studies aimed at determining whether or not WCH is accompanied by organ damage or alterations in cardiovascular structure. Some investigators reported that patients with WCH have a different metabolic and neuroendocrinic profile [10], increased left ventricular mass [11, 12], impaired diastolic [13] and endothelial function [14, 15]. In contrast, several other studies have suggested that WCH is not associated with alterations in cardiac structure (as well as other types of organ damage, including endothelial dysfunction or microalbuminuria) and no significant differences exist between "white coat hypertensives" and normotensive subjects regarding these parameters [16-18].

It has been previously shown that essential hypertension is associated with abnormalities in haemostatic/fibrinolytic balance and endothelial function, indicated by alterations in plasma levels of fibrinogen, plasminogen activator inhibitor (PAI), tissue plasminogen activator (tPA) and thrombomodulin [19-22]. Recent evidence is accumulating that many of these markers are predictors of future vascular events, both ischemic heart disease and stroke [23, 24]. Only few previous studies have examined a potential association between WCH and these parameters [25-27]. The aim of our study was to investigate whether WCH affects plasma levels of haemostatic/fibrinolytic and endothelial function markers, including plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator antigen (tPA), fibrinogen, and thrombomodulin.

PATIENTS AND METHODS

This study was performed in Greek patients who attended the Hypertension Clinic of our hospital. The study was approved by our institutional review committee and informed consent was obtained from each subject studied.

BP was measured in the sitting position in a quiet room, using a mercury sphygmomanometer, after the patient had rested for at least 10 minutes. Systolic BP was recorded at the appearance of sounds (Korotkoff phase I) and the diastolic at their disappearance (Korotkoff phase V). No patient had ever received antihypertensive therapy. A detailed history was obtained and physical examination and electrocardiogram were conducted on each subject. Heart rate was measured from a standard electrocardiogram under the same conditions and calculated as the average of nine R-R intervals. Patients with CAD, secondary hypertension, renal failure, liver disease or other serious illness were excluded from this study; smokers were defined as current smokers. Alcohol consumption was determined by a questionnaire which asked for the information about the daily consumption of wine, liquor and beer; alcohol intake was expressed in grams per day. Information concerning physical activity was obtained from questionnaires that have been previously described [28]. Subjects were weighed (kg), and height (m) was measured wearing only light clothing without their shoes. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Essential hypertension (EH) was diagnosed when the systolic BP was ≥ 140 mmHg and/or the diastolic BP was ≥ 90 mmHg on at least three separate occasions [1, 2]. The reported office BP values represent the average of three measurements in every visit, obtained on at least three separate occasions, within three weeks. One hundred twelve (n = 112) patients who fulfilled these BP criteria, as well as 87 control subjects, underwent non-invasive ambulatory BP monitoring (ABPM) with Spacelabs 90207, which recorded BP every 20 minutes during daytime (between 10:00 AM and 8:00 PM) and 40 minutes during nighttime (between midnight and 6:00 AM) for 24 hours. Subjects recorded a daily action profile from which information about the precise times of sleeping and waking were obtained. The onset of sleep was identified as the time that the subject went to bed. The subjects were instructed to carry out normal daily activities during the monitoring period. Blood samples were obtained for determination of blood lipids and haemostatic factors in all these subjects, as well as in a control group of healthy volunteers who also underwent ABPM. Control subjects (n = 87) were recruited while they were submitted to preoperative (mainly orthopaedic, ophthalmologic, etc.) cardiac examination few days prior to surgery. They were included if they were normotensive (clinic blood pressure within normal values), with no other serious illnesses, and none of them was receiving any medication known to interfere with the studied parameters (including HRT, statins, aspirin, etc.). According to the results of clinic and ABPM blood pressure measurements, patients were classified into a group of WCH, if clinic BP was ≥ 140 mmHg and/or the diastolic BP was ≥ 90 mmHg, while 24-hour average ABPM levels were found less than 125/80 mmHg [1, 2], hypertensives, if clinic and ABPM values were found greater than these levels and normotensive, with both clinic and ABPM values lower than these levels. Venous blood samples were collected without stasis after 10 minutes supine rest. Participants were instructed to avoid strenuous physical activity and not to smoke tobacco during the hour preceding this examination, which took place between 8 and 9 am, to reduce interference by the diurnal variation of PAI-1. All subjects had fasted for at least 12 hours.

PAI-1 Ag, tPA Ag, and thrombomodulin were determined with an enzyme linked immunosorbent assay (ELISA), (Diagnostica Stago, Asnieres, France). Fibrinogen levels were measured with Claus technique. Serum cholesterol and triglyceride levels were determined by an enzymatic method and low density lipoprotein (LDL) was calculated according to the Friedwald formula, since no subject had a triglyceride level higher than 400 mg/dL.

Statistical analysis

Values are expressed as the mean ± SD. Differences between the three groups were analysed by one way analysis of variance (ANOVA). The variables that showed significant differences were compeared afterward between each group by use of Bonferroni test for multiple comparisons. The correlations between variables were determined by use of Spearman correlation coefficient. A p value of < 0.05 was accepted as statistically significant.

RESULTS

Five patients out of 112 that were initially enrolled were excluded from the study due to inadequate ABPM recordings. Twenty-six out of 107 initially classified as hypertensive patients (24,3%) were found to be white coat hypertensives. Clinic and ambulatory BP values are presented in *table 1*. Ten more subjects from the hypertensive group were excluded due to inadequate blood samples. Finally, haemostatic/fibrinolytic parameters were determined in 71 patients with confirmed essential hypertension, 26 with WCH and 87 healthy normotensives. The three groups were not different with respect to age, gender, BMI, smoking status, and lipid profile *(table 1)*. No differences were observed between the three groups regarding physical activity, alcohol consumption and menopausal status (data not shown).

The haemostasis balance parameters for each group are shown in *table 2*. The PAI-1 Ag, tPA-Ag, fibrinogen and thrombomodulin levels were significantly higher in the hypertensive group than in white coat hypertensives. Subjects with WCH were found to have signifantly higher plasma levels of PAI-1 Ag, tPA-Ag, fibrinogen and thrombomodulin compared to the normotensive control group *(table 2)*. The differences remained significant even after Bonferroni correction (Bonferroni adjusted $\alpha = 0.01$).

Correlation analysis showed that in the EH group fibrinogen levels correlated significantly with BMI and triglycerides ($r = 0.521$, $p = 0.001$, $r = 0.351$, $p = 0.01$, respectively), PAI-1 correlated significantly with BMI, SBP, LDL and triglycerides ($r = 0.121$, $p = 0.05$, $r = 0.235$, $p = 0.01$, $r = 0.123$, $p = 0.001$, $r = 0.541$, $p = 0.01$ respectively), tPA with DBP ($r = -0.323$, $p = 0.001$). In the WCH group fibrinogen levels correlated significantly with BMI ($r = 0.452$, $p = 0.01$), PAI-1 correlated significantly with BMI, SBP, and triglycerides ($r = 0.312$, $p = 0.01$, $r = 0.224$, $p = 0.01$, $r = 0.537$, $p = 0.01$, respectively), thrombomodulin with DBP ($r = 0.465$, $p = 0.01$). In the normotensive group fibrinogen levels correlated significantly with triglycerides ($r = 0.234$, $p = 0.01$), PAI-1 correlated significantly with BMI, SBP, DBP and triglycerides ($r = 0.239$, $p = 0.001$, $r = 0.387$, $p = 0.01$, $r = 0.353$, $p = 0.01$, $r = 0.137$, $p = 0.001$, respectively), thrombomodulin with LDL ($r = -0.246$, $p = 0.01$).

Table 1
Demographic data, clinical and lipidemic profile for each group

	EH (n = 71)	**WCH** (n = 26)	**Norm** (n = 87)	**p**
Age	56.2 ± 3.9	56.8 ± 4.3	55.9 ± 4.2	NS
Male sex	24 (57.1%)	16 (53.3%)	17 (53.1%)	NS
Smokers	15 (35.7%)	9 (36.6%)	11 (34.3%)	NS
BMI (kg/m^2)	25.0 ± 1.7	24.9 ± 2.0	24.5 ± 2.0	NS
Clinic SBP (mmHg)	162 ± 2.7	161 ± 1.9	121 ± 6.7	0,001 §
Clinic DBP (mmHg)	98 ± 3.2	96 ± 2.5	80 ± 3	0,001 §
Mean ambulatory SBP	152 ± 4.3	119.0 ± 6.7	118.0 ± 5.9	0,001 *§
Mean ambulatory DBP	95 ± 5.3	77 ± 2.8	76 ± 3.1	0,001 *§
Heart rate (beats/min)	78 ± 2.6	76 ± 3.4	77 ± 2.8	NS
Total cholesterol (mg/dL)	231.7 ± 22.5	233.2 ± 26.3	231.9 ± 25.1	NS
HDL (mg/dL)	40.8 ± 5.2	42.8 ± 5.8	41.8 ± 3.7	NS
LDL (mg/dL)	158.4 ± 24.6	160.3 ± 30.5	156.9 ± 27.1	NS
Triglycerides (mg/dL)	97.1 ± 27.3	99.9 ± 31.6	102.8 ± 31.9	NS

EH: essential hypertension, WCH: white coat hypertension, Norm: normotensives. Mean ± SD or n (%) is shown. NS: not significant. * Significant differences between EH and WCH. § Significant differences between EH and normotensives.

DISCUSSION

The results of our study have shown that WCH is associated with increased plasma levels of PAI, tPA, fibrinogen, and thrombomodulin compared to normotensives, indicating a decreased fibrinolytic capacity and endothelial damage, although this effect is expressed to a lesser extent compared to patients with EH. The question of whether this group of WCH has an increased cardiovascular risk similar to that of sustained EH, or similar to that of normotensive subjects is an interesting and unresolved issue that could entail therapeutic implications, considering that prevalence of WCH varies from 15% to 35% among the population of hypertensives [3]. Most previous studies have reported a cardiovascular event rate similar to that of normotensive individuals [3-6], however, others have suggested that WCH may be associated with an increased total and cardiovascular mortality [7-9]. The prevalence of WCH, defined as ABPM levels ≤ 125/80 mmHg [1, 2], was found to be 24,3% in our study group, which is similar to that reported by other studies[3]. Previous studies aimed at investigating whether WCH is accompanied by organ damage or, more important, by an adverse prognosis, have provided inconsistent conclusions, probably originating from the different cutoff point chosen to define a hypertensive clinic pressure and a normal ambulatory pressure, or from the different characteristics of the patients recruited in several studies.

Our results have shown that WCH is related with increased plasma levels of PAI and tPA Ag compared to normotensive subjects, but to a lesser extent compared to patients with EH. These results are consistent with a recent study [25], which also found inreased levels of PAI in subjects with WCH compared to normotesives. This finding indicates that in our study population WCH is associated with a state of decreased fibrinolytic capacity, which may potentially contribute to an increased incidence of cardiovascular events in this group.

We also found increased levels of fibrinogen in white coat hypertensives compared to normotensive ones, but lower than in patients with EH. Our finding is in concordance with a previous study conducted by Coban *et al*. [26]. Fibrinogen is a major determinant of blood viscosity and it is also involved in haemostasis/thrombosis pathways. Fibrinogen levels have been shown to be an independent predictor of subsequent cardiovascular events [23, 24], underlining the clinical significance of this result.

The impact of WCH on thrombomodulin plasma levels was also put under examination. Thrombomodulin (TM) is a protein cofactor expressed on endothelial cells of most blood vessels. Thrombin-bound TM activates protein C, which inhibits thrombin generation by degrading factors Va and VIIIa. TM has also been proposed as a marker of endothelial cell damage and alterations in TM plasma levels have been found to be associated with EH and atherosclerosis [29, 30]. We found that TM levels are greater in white coat hypertensives than in control group, but lower than in subjects with EH. Although the precise mechanisms of TM regulation are not yet quite clear, it has been suggested that an EH mediated damage consequently results in endothelial release of this marker [30]. Our results are not in line with a previous report by Kario *et al*. [27], which did not show any significant differences

Table 2
Haemostatic balance parameters for each group

	EH (n = 71)	**WCH** (n = 26)	**Norm** (n = 87)	**p**
Fibrinogen (mg/dL)	330 ± 51	300 ± 50	287 ± 40	0,015*§
PAI-1 Ag (ng/mL)	7,6 ± 0,9	6,5 ± 0,7	6 ± 0,8	0,023*§
tPA-Ag (ng/mL)	9,1 ± 1,2	8,5 ± 1,3	7,8 ± 0,7	0,003*§
Thrombomodulin (ng/mL)	26 ± 8	22 ± 10	18 ± 11	0,018*§

EH: essential hypertension, WCH: white coat hypertension, Norm: normotensive. Values are mean ± SD. * Significant differences between EH and WCH. § Significant differences between EH and normotensives.

regarding TM levels between "normoalbuminuric" hypertensives, white coat hypertensives and normotensive control subjects. It is interesting that several previous studies examining a potential association between WCH and other indices of endothelial function, including microalbuminuria, endothelial dependent vasodilation, or alterations in other endothelium derived factors (von Willebrand factor, endothelin, etc), have also provided contradictory results with some confirming [24, 15] and others rejecting [16, 17, 27] this relation. It is possible, however, that the aforementioned differences regarding study population and WCH definition may have been responsible for this discrepancy. While it has been previously shown that essential hypertension is often associated with decreased fibrinolytic potential, procoagulant tendency and endothelial cell damage [19-22], the responsible pathways to this association remain controversial. This has been occasionally attributed to endothelial damage induced by increased blood pressure [31] or to several features of the metabolic syndrome [32]. It must also be noted that these abnormalities have been observed in normotensive offspring of hypertensives or in hypertensive-prone subjects, indicating the contribution of other factors, unrelated to blood pressure values, including metabolic, neurohumoral and genetic factors as well [33-35]. Finally, endothelial dysfunction and activation of procoagulant factors, well established to be related to each other, have been previously described in subjects with WCH [14, 15, 25, 26]. These data may provide a plausible explanation for the haemostatic abnormalities observed in white coat hypertensives (compared to normotensives), although BP remains within normal values throughout 24 hours.

It has been suggested that WCH may simply be a precursor of sustained hypertension. Although the literature in this issue is inconsistent at present, some studies have found a higher risk of developing sustained hypertension [8, 36-39]. Taken these into account, the results of our and other studies that have shown cardiovascular alterations related to WCH, may indicate that these subjects should undergo a complete assesment of possible organ damage and overall cardiovascular risk. If, in the absence of cardiac orother organ damage drug treatment is not implemented, a follow-up of these patients is nevertheless advisable, since a greater tendency toward cardiovascular alterations or progression to sustained hypertension cannot be excluded [12, 38, 39].

It should be mentioned that the small sample size may represent a limitation of our study.

In conclusion, our study showed that subjects with white coat hypertension have increased plasma levels of PAI, tPA, fibrinogen, and thrombomodulin compared to normotesives, indicating a procoagulant tendency and endothelial damage. Therefore, WCH may not be a completely harmless trait, indicating the necessity of estimating the overall risk in white coat hypertensives.

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