



ORIGINAL ARTICLE

Is elevation of clinic blood pressure in patients with white coat hypertension who have normal ambulatory blood pressure associated with target organ changes?

PE Owens¹, SP Lyons¹, SA Rodriguez² and ET O'Brien¹

¹Blood Pressure Unit, Beaumont Hospital, Dublin 9, Ireland; ²University Hospital Maastricht, Department of Internal Medicine, Maastricht, The Netherlands

Background: The issue as to whether white coat hypertension is a pathologically significant entity, with associated target organ changes, or that the condition carries the same risk for target organ involvement as normotension, is undecided. Previous studies which have shown pathological correlates between white coat hypertension and target organ damage have not controlled for the most obvious confounder, mean 24 h blood pressure (BP).

Methods and results: In this study we retrospectively identified 33 age and sex-matched pairs, one group with normal BP, the other with white coat hypertension. The white coat hypertensive group showed significantly greater left ventricular mass indexed for body surface area than normal controls (99.0 g/m² vs 78.3 g/m², $P <$

0.001). The population was then further matched for 24-h mean BP (20 pairs), and was again compared for cardiac muscle changes. The significantly increased left ventricular mass index in the white coat population remained after controlling for 24-h mean BP (101.1 g/m² vs 81.0 g/m², $P <$ 0.021).

Conclusion: White coat hypertension is indeed associated with a larger left ventricular muscle mass than normotensives and these changes are independent of the actual 24-h BP load, and may reflect increased BP lability, sympathetic nervous system derangement, or a genetic propensity in people with white coat hypertension to stress-related hypertensive reactions, as part of a pre-hypertensive state.

Keywords: white coat hypertension; ambulatory blood pressure monitoring; left ventricular hypertrophy; echocardiography; target organ damage

Introduction

White coat hypertension has long been recognised as an acute elevation of blood pressure (BP) occurring in the context of active third party BP measurement.¹ Various terms 'white coat hypertension', 'clinical hypertension', or 'isolated clinic hypertension'² (we will herein refer to the phenomenon as white coat hypertension (WCH)), it has been assumed that the lack of sustained hypertension in these patients reflects a reactive sympathetic nervous system, and predicts a benign prognosis. A number of studies looking at evidence of target organ damage have given equivocal results; left ventricular hypertrophy and renal dysfunction have both been described as occurring in association with WCH,³⁻⁸ while other studies have not documented an association.⁹⁻¹² These studies have largely shown significantly higher mean UP in the WCH group, and it may be that the documented elevation of cardiac and renal indices of end-organ involvement found

in these studies are simply a reflection of this higher BP in this group.¹³

In this case-control study, we identified a large cohort of patients with WCH defined on 24-h ambulatory BP (ABP) monitoring, and an age and sex-matched normal cohort drawn from the normal population. Groups were compared for ABP profiles, and the presence of target organ involvement, namely the presence of myocardial hypertrophy. The groups were then further matched for 24-h mean arterial UP, and the comparison for left ventricular mass index (LVMI) was then repeated, to determine if controlling for BP differences between the populations would remove the perceived differences in target organ involvement.

Subjects and methods

Patient population

Patients were identified from a search of the database in the Blood Pressure Unit (Beaumont Hospital, Dublin, Ireland) which comprises patients referred to the hospital for investigation of hypertension. Patients referred to this service routinely have electrocardiography and echocardiography performed

within 1 week of the ABP monitor being applied. Patients were selected if they met with the following definition of WCH, namely an elevation of the clinic BP, with or without an elevation of the initial BP (first hour) on the ABP monitor above 140 mm Hg systolic and/or 90 mm Hg diastolic, with a normalisation of the BP to below these figures within the next hour, and a subsequently normal BP mean for both daytime (systolic <135 mm Hg, diastolic <85 mm Hg) and night-time (systolic <125 mm Hg, diastolic <70 mm Hg) monitoring periods. Patients were excluded if the above definition was not met, or if the routine screening tests were not performed. Also, patients were not included if they were documented as taking antihypertensive medication at any time prior to referral for the ABP monitor. Shift workers were excluded from the analysis.

Control population

Control patients were enrolled from a database of ABP in the normal population, the initial study of which has been described elsewhere.¹⁴ Patients from this population have been routinely brought back for follow-up study, from 1995 onward, and had electrocardiography and echocardiography performed on the day of the ABP monitor. A total of 130 control subjects were available for cross-matching. WCH patients were assigned age and sex-matched controls from this database. The matching procedure was undertaken without knowledge of the patients BP variables, by a physician told only: (1) which patient cohort the subject belonged to; and (2) age and sex. Only controls with a normal clinic, initial, daytime and night-time ABP profile according to the above definition were enrolled. Again, patients were excluded if the screening data was deficient, or if they were taking medicines known to interfere with UP.

Echocardiography

Echocardiography was performed by a trained echocardiographer using a standard 2.5 MHz echocardiography transducer applied to the chest in the parasternal long and short axis planes, where measurements of wall thickness, and chamber size were made. To ensure there was no systematic observer bias, three M-mode tracings were printed from each of the videotaped studies; a trained technician then manually measured the chamber parameters, blinded to the case-control status of the patients, and took the mean dimensions for the three tracings as the measured variable. The left ventricular mass was calculated from these parameters using the formula of Devereux *et al.*¹⁵ This was subsequently indexed for body surface area.

Blood pressure measurement

Clinic BP was measured in accordance with the recommendations of the British Hypertension Society.¹⁶ For controls, all readings were required to be below 140/90 mm Hg systolic and 90 mm Hg diastolic. All case patients had an elevated clinic BP on

referral from their general practitioner, and all had an elevated clinic BP again when measured in the Blood Pressure Unit prior to the affixing of the ABP monitor. The clinic pressures were measured in both cases and controls (after 5 min quiet sitting) by the Unit nurse, prior to affixing the ABP monitor. The lower reading was taken as the clinic pressure, and this value was entered into the database.

Twenty-four ABP measurement was performed using the SpaceLabs 90207 (Redmond, WA, USA) ABP monitor.¹⁷ Monitors were programmed to measure BP at 30-min intervals day and night. The monitor was removed the next day, and the data was transferred into a personal computer and loaded into a specialised software package (DABL).¹⁸ The initial, daytime and night-time systolic, diastolic and mean BP were calculated. The 'daytime period' was defined as the hours between 09.00 and 21.00 hours (excluding the initial period), and night-time as the hours between 01.00 and 06.00 hours. The 24-h period was defined as the total period of measurement time from application to removal of the monitor. Transition times (21.01 to 00.59 hours, and 06.01 to 08.59 hours) were not included in the estimation of day and night mean pressures, as these periods represent times during which bed rest is inconsistent and therefore cannot reliably be categorised.¹⁹ Patients on night shift work, or within 4 weeks of completing night shift duty, were not included in the analysis. Recordings were not included if there were less than 14 valid readings during the day, or less than seven valid readings during the night. The validity criteria were those identified by the editing software, ie, systolic BP < diastolic BP, diastolic BP >160 or <40 mm Hg, systolic BP >260 or <50 mm Hg. BP values not identified by the editing software were included in the analysis.²⁰

Definitions and statistics

Clinical data was extracted from the database, in accordance with the following definitions. Family history of hypertension was defined as the reporting of hypertension in a first degree relative. A family history of vascular disease was present if one or more first degree relatives had suffered a myocardial infarction, angina pectoris, a cerebrovascular accident or had been given a diagnosis of peripheral vascular disease. The presence of any other medical condition identified from the clinical review at time of monitoring was considered a potential confounder and this patient's record was not included in the analysis.

The initial matched groups were compared for BP variables, and for left ventricular mass; the pairs were then further matched for BP by assigning a sex-specific sequential ranking code to the mean 24-h BP for subjects in each group. The ranked pairs obtained were then compared for actual BP and age; corresponding BP values and age not differing by 2.5 mm Hg and 2 years were deemed acceptably paired and this pairing was included in the age, sex and BP matched cohort. The secondary selection procedure

Table 1 Clinical characteristics of age and sex-matched patient population. Values are expressed as the mean (95% confidence intervals for the mean)

	Cases	Controls	P value
<i>n</i>	33	33	
Age (yrs)	40.3	40.1	
Sex (M/F)	9/24	9/24	
Weight (kgs)	73.6 (67.9–79.4)	70.0 (65.9–74.1)	0.20
Height (cm)	166.6 (162.8–170.4)	168.8 (165.8–171.7)	0.23
Family history of hypertension	21/33	15/33	NS
History of vascular disease	15/33	17/33	NS
Smoker	13/33	13/33	NS

was undertaken by an observer blinded to the left ventricular mass measurements of the cohort.

Group differences between variables was explored using the paired *t*-test. Where non-normal data was compared, the Wilcoxon Rank Sum method was used. Differences in proportions between paired variables were explored by calculation of the *z* statistic. A *P* value of less than 0.05 was considered significant.

Results

Age and sex-matched population

A total of thirty-three age and sex-matched pairs were identified. The clinical data between groups are presented in Table 1. WCH patients were slightly heavier than controls, but not significantly so. Body mass index (BMI) was comparable across the two groups. A family history of hypertension was found more frequently in the WCH patient population, but there was no difference in reported family history of vascular disease. The incidence of cigarette smoking was comparable between the IWO groups.

Intra-observer error for echocardiographic parameters was small; ANOVA testing showed no overall difference in the mean LVM calculated from the three sets of measurements. Absolute differences across measurements did differ significantly from zero, with a mean difference of 2.4 grams (95% confidence interval 2.0–2.8). Accordingly, although significant, the absolute intra-observer variability was small.

The data pertaining to ABP are presented in Table 2. By definition, WCH patients had a significantly higher initial systolic and diastolic BP. Daytime and night-time systolic BPs were significantly higher in the WCH patient group, although remaining within

the normal range. There was no difference between the groups with respect to presence of nocturnal dipping of BP or heart rate. The LVMI is presented in Table 2. Both groups showed a LVMI within the normal range (<110g/m²), but the LVMI for white coat hypertensives was significantly greater than controls.

Age, sex and blood pressure matched population

Secondary matching identified 20 age, sex and BP matched pairs. BMI was not significantly different between the groups, and they were comparable for other clinical features (Table 3). The BP data are presented in Table 4. The groups were similar for 24-h BP parameters, and only differed in the initial BP profile, with the WCH group having a higher initial systolic and diastolic pressure. End-organ data from the two groups shows persistence of the differences in left ventricular muscle mass index (Table 4), with the WCH group demonstrating significantly higher LVMI. A multiple regression model was fitted to the data with LVMI as the dependent variable, to determine possible confounding by the independent variables daytime and night-time systolic and diastolic BP, age, BMI, height, weight and sex. Additionally, the presence or absence of WCH was entered into the model as a covariate. The only significant predictors in the model were the presence or absence of WCH (*P* = 0.011), and age (*P* = 0.01).

Discussion

White coat hypertension as a clinically distinct entity has been recognised for some time.^{21,22} As many as 20% of patients presenting for ABP moni-

Table 2 Blood pressure and left ventricular mass data from age and sex-matched cases and controls. All BP data are expressed as mm Hg. Data values are expressed as means (95% confidence intervals for the mean)

	Cases	Controls	P value
Clinic SBP	162.2 (157.8–166.5)	110.6 (106.1–115.1)	<0.0001
Clinic DBP	102.0 (98.9–105.1)	69.6 (66.7–72.5)	<0.0001
Day SBP	125.4 (123.3–127.5)	117.1 (113.8–120.3)	<0.001
Day DBP	77.6 (76.0–79.2)	75.0 (72.9–77.1)	0.051
Night SBP	101.6 (98.9–104.3)	106.9 (104.0–109.8)	0.01
Night DBP	62.9 (60.8–64.9)	60.5 (58.5–62.4)	0.09
LVMI (g/m ²)	99.0 (88.2–109.8)	78.3 (71.3–85.3)	0.001

Table 3 Clinical characteristics of age, sex and BP-matched patient population. Values are expressed as the mean (95% confidence intervals for the mean)

	Cases	Controls	P value
n	20	20	
Age (yrs)	90.2	40.8	
Sex (M/F)	10/10	10/10	
Weight (kgs)	79.9 (72.5-67.4)	75.0 (70.0-80.0)	0.14
Height (cm)	170.5 (165.5-175.6)	173.1 (169.2-176.9)	0.37
Family history of hypertension	5/20	5/20	NS
History of vascular disease	9/20	10/20	NS
Smoker	8/20	9/20	NS

Table 4 Blood pressure data from age, sex and BP-matched cases and controls. All BP data are expressed as mm Hg. Data values are expressed as means (95% confidence intervals for the mean)

	Cases	Controls	P value
Clinic SBP	160.2 (154.6-165.8)	116.2 (111.5-120.9)	<0.0001
Clinic DBP	102.3 (98.1-106.5)	73.0 (70.2-75.8)	<0.0001
Day SBP	125.2 (122.2-128.0)	123.0 (120.3-125.8)	0.17
Day DBP	77.2 (75.0-79.4)	78.8 (76.8-80.8)	0.18
Night SBP	108.0 (104.7-111.3)	105.3 (102.9-107.7)	0.10
Night DBP	63.1 (60.6-65.7)	62.8 (60.7-64.9)	0.81
LVMI (g/m ²)	101.1 (87.2-115.0)	81.0 (70.6-91.5)	0.021

SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

toring with an elevated clinic measured BP may have a normal 24-h BP profile.²³ The debate continues as to whether the clinical condition of WCH represents a true pathological state, with associated morbidity, or a benign manifestation of a reactive sympathetic nervous system.²⁴

There has been recent speculation that WCH is not an entirely benign entity. Left ventricular mass has been shown to be higher in elderly white coat hypertensives than in normal controls.^{4,7} However the literature is at variance on the subject, with other reports suggesting that no significant left ventricular remodelling occurs in these patients.¹¹ It is interesting to note that previous comparative studies of WCH vs normotension have shown higher 24-h BPs in the WCH group.^{6,7,11} This would at least suggest that within the normal range, WCH patients have a higher 24-h BP load, occupying a higher pressure stratum than normotensives. The subtle changes in left ventricular mass could be accounted for by this BP discrepancy.¹³ If this was the case, then one would expect that differences between normo- and white coat hypertensives with regard to target organ changes would disappear when the groups are further controlled for 24-h BP. Indeed, two such studies,^{9,10} comparing left ventricular mass between normotensive and WCH groups, where 24-h BP was comparable across the two groups, showed no difference in structural heart changes. On the other hand, Glen *et al*⁹ in a similarly designed study, with 131 equivalence between the normal and WCH groups, showed evidence of functional cardiac derangement in the WCH group. This last study has however been criticised for having a very high cut-off point for the difference between normotension and hypertension, at 95 mm Hg diastolic.^{25,26} As discussed by Verdecchia *et al*,²⁷ a high cut-off point may result in

patients with borderline hypertension being included in the definition of WCH. As a result, end-organ damage may be ascribed to patients given the qualitative diagnosis of WCH, when in fact it is the quantitative, continuous variable of BP that is responsible for end-organ changes. Our study specifically compares cardiac muscle mass between normal patients and white coat patients, and removes the possible confounding effect of differences in BP between the two groups. The fact that differences in muscle mass persisted when BP differences were removed from the equation is strong evidence that white coat hypertensives are indeed different from their normotensive counterparts.

Left ventricular hypertrophy (LVH) has been well documented as an indicator of a poor prognosis in patients with hypertension.²⁸ It is possible that even with our strict matching of BP, minor differences in measured pressure might, over a protracted time period, give rise to the observed differences in left ventricular mass, but the minimal differences between the populations would make this very unlikely.

What aetiological mechanisms may be at work to cause cardiac changes in the presence of WCH but in the absence of sustained elevation of BP? Firstly, transient stress-related increases in BP, occurring throughout the course of the day may account for reactive changes in the vascular architecture of the heart, while not altering the mean BP load, as measured on 24-h ABP monitoring. Thus, an increase in BP variability may account for the changes in target organs.²⁹ However, a number of studies have failed to show significant BP lability in patients with WCH.^{30,31} Secondly, the presence of WCH may be a manifestation of an underlying dysfunctional sympathetic nervous system.^{32,33} Left ventricular muscle

