Relationships Between Ambulatory White Coat Effect and Left Ventricular Mass in Arterial Hypertension

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The aim of our study was to analyze, in a group of 296 essential hypertensives, the relationship between left ventricular mass (LVM) and ambulatory white coat effect (WCE); that is the difference between the elevation of the first measurements of ambulatory blood pressure monitoring and the mean daytime pressure.

The study population was separated into two groups according to the median of the WCE. The LVM was greater in the groups with higher systolic and diastolic ambulatory WCE. The significant association between ambulatory WCE and LVM was confirmed by the results of multiple regression analysis, suggesting that ambulatory WCE may not be an innocent phenomenon. Am J Hypertens 2003;16:498–501 © 2003 American Journal of Hypertension, Ltd.

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I t has long been recognized that measurement of blood pressure (BP) in the clinic environment may trigger an alerting reaction in the patient that is often characterized by a marked and fast BP increase.[1] This pressor response may be directly recorded through intraarterial or noninvasive techniques that allow a beat-by-beat measurement of BP, but is routinely estimated simply by subtracting the daytime average BP, evaluated by ambulatory BP monitoring (ABPM) or by home BP self-monitoring, from the clinic BP or by determining the physician–nurse difference in BP measurements. More recently, Owens et al[2] proposed an alternative definition of the white coat effect (WCE) based solely on ABPM, that is the difference between the maximum BP during the first or last hour of ABPM and the daily mean BP. This proposal is based on the common finding of elevated BP readings in the first or last hour of an ABPM, as compared to the remaining daytime period. This elevation, that has been called ambulatory WCE, probably reflects the stress due to the unfamiliar environment and staff at the clinic during the application and removal of the monitoring device.[2] Little is known about clinical and prognostic implications of ambulatory WCE.[2]

The present study was undertaken to evaluate the relationships between ambulatory WCE, defined in a way similar to that suggested by Owens et al,[2] and left ventricular mass in a group of essential hypertensives.

Methods

The study population consisted of 320 consecutive outpatients attending our institution. All of them were undergoing for the first time ABPM as part of clinical assessment of their hypertension. The subjects recruited had mild-to-moderate essential hypertension, defined according to clinic BP. Before entering the study, 276 hypertensives had been pharmacologically treated. These patients were studied after the discontinuation of all antihypertensive drugs for at least 2 weeks.

Written informed consent was obtained from each patient.

After the period of pharmacological washout, body weight and height were measured and clinic BP recorded on three separate occasions. Moreover, all patients underwent 24-h ABPM and an echocardiographic study.

Twenty-four of the 320 patients were excluded from the study because BP exceeded 180/110 mm Hg during the washout period or because suboptimal echocardiographic
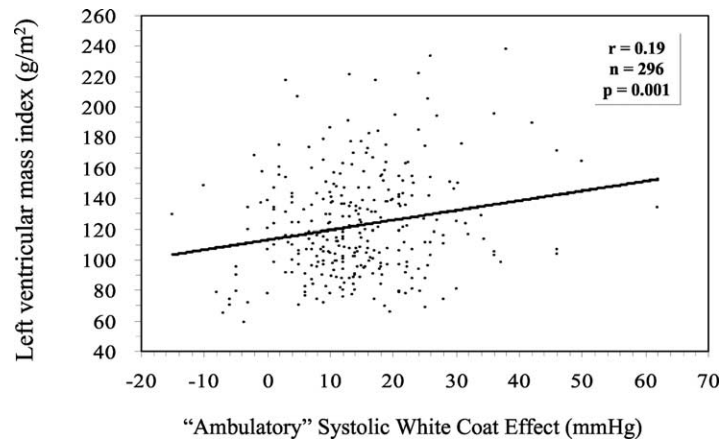
FIG. 1. Correlation in the whole study population between left ventricular mass index and "ambulatory" systolic white coat effect (defined as the difference between the first ambulatory blood pressure monitoring systolic reading and the mean daytime systolic blood pressure).

tracings or fewer than 80% valid ABPM measurements were obtained.

M-mode echocardiography, guided by a two-dimensional echocardiography, was performed with the patient maintained in a partial left decubitus position, using an SPR Esaote 8000 Instrument (Esaote, Firenze, Italy). Echocardiographic data are expressed as the average of five consecutive cardiac cycles. M-mode measurements were taken according to the American Society of Echocardiography recommendations.[3] Left ventricular mass (LVM) was determined using the autopsy-validated Devereux's formula,[4] which was indexed for body surface area (LVMI).

A portable, noninvasive SpaceLabs 90207 recorder (Redmond, WA) performed the 24-h ABPM. The device was applied in the morning and removed the next day at our hypertension unit. Initially, three different definitions of ambulatory WCE, for both systolic and diastolic values, were used: difference between the first ABPM reading and the mean daytime pressure (WCE 1); difference between the mean of first hour of ABPM and the mean daytime pressure (WCE 2); and difference between the maximum pressure in the first or last hour of ABPM and the mean daytime pressure (WCE 3). Subsequently, the relationships of left ventricular (LV) mass index with each of these different ways to define ambulatory WCE were tested by Pearson's correlation coefficients. Because the first definition (WCE 1) showed the closest correlations with LVMI, in the following analyses of our study WCE was considered only in this way, namely the difference between the first measurement of ABPM and the mean daytime pressure. Therefore, the study population was separated into two groups according to the median of the WCE 1, for both systolic and diastolic values.

Continuous variables were given as means ± SD. Differences between groups with higher and lower ambulatory WCE were evaluated using the Student t test for unpaired data. Adjustment for some confounding variables was made by analysis of covariance. For the categorical variables, comparisons were carried out using the χ^2 test. Simple and multiple regression analyses were performed to assess the influence of ambulatory WCE on LVMI. All the variables showing a statistically significant association with LVMI in the univariate analysis were considered to build a multiple linear regression model. The null hypothesis was rejected at a two-tailed $P \leq .05$.

Results

The mean age of our study population was 46.5 ± 10.6 years. The population comprised 169 men and 127 women. Ambulatory WCE defined as the difference between the first ABPM reading and the mean daytime pressure (WCE 1) was 14.2/13.4 ± 10.3/8.1 mm Hg for systolic and diastolic values, respectively. The WCE 2 (see methods section for definitions) was 9.6/9.8 ± 8.8/6.7 mm Hg and WCE 3 was 23.1/19.6 ± 10.5/7.3 mm Hg. Of these definitions of WCE, the former showed the closest correlations, in univariate regression analysis, with LVMI (for systolic values, $r = 0.19$; $P < .001$; Fig. 1; for diastolic values, $r = 0.16$; $P < .01$).

The coefficients of correlation between WCE2 and LVMI were 0.10 (P = NS), both for systolic and diastolic parameters, and those relative to the relationships between WCE3 and LVMI were 0.14 ($P <.05$), both for systolic and diastolic readings. Therefore, from now onward, only WCE1 was used in the analyses on the relationships between ambulatory WCE and LVM.

The patients with systolic WCE above the median (13.5 mm Hg) were older (48.6 ± 9.8 v 44.4 ± 11.1 years, P = .001) and showed a tendency toward a longer duration of hypertension (75.7 ± 67.6 v 62.5 ± 60.7 months; P = .07) in comparison with the subjects with a shorter duration. Clinic systolic BP was higher (168.8 ± 17.9 v 154.8 ± 14.6 mm Hg; P = .001) and ambulatory mean daytime systolic BP was lower (140 ± 10.2 v 142.3 ± 10.7 mm Hg; P = .05), in the subset with a greater systolic WCE. Furthermore, in this latter group a greater daytime systolic

Table 1. Cardiac parameters of the subject groups divided according to the median of systolic and diastolic white coat effect (WCE)

	Systolic WCE < 13.5 mm Hg (*n* = 148)	Systolic WCE > 13.5 mm Hg (*n* = 148)	*P*	*P**	Diastolic WCE < 15 mm Hg (*n* = 148)	Diastolic WCE > 15 mm Hg (*n* = 148)	*P*	*P*†
LVIDd (mm)	49.5 ± 6.2	49.1 ± 5.5	NS	NS	49.1 ± 6.2	49.4 ± 5.6	NS	NS
IVSd (mm)	10 ± 1.6	10.6 ± 2.1	.01	.03	9.8 ± 1.7	10.8 ± 1.9	.001	.001
PWTd (mm)	9.6 ± 1.6	10.2 ± 1.8	.008	.01	9.6 ± 1.6	10.2 ± 1.8	.003	.001
RWT	0.39 ± 0.09	0.42 ± 0.09	.02	.03	0.40 ± 0.09	0.42 ± 0.09	.04	.05
LVMI (g/m^2)	117.2 ± 31.3	127.2 ± 35.7	.01	.04	115.5 ± 32.1	128.8 ± 34.3	.001	.001

(d) end-diastolic; LVIDd = left ventricular internal dimension; NS = not significant; IVSd = interventricular septum thickness; PWTd = posterior wall thickness; RWT = relative myocardial wall thickness; LVMI = left ventricular mass index.

* Adjusted by ANCOVA for age, duration of hypertension, and mean daytime systolic blood pressure.

† Adjusted by ANCOVA for gender, duration of hypertension, and mean daytime diastolic blood pressure.

Systolic and diastolic WCE was considered as the difference between the first measurement of ambulatory blood pressure monitoring and the mean daytime pressure.

variability, expressed by the standard deviation (SD) from the average BP value, was observed (13.4 ± 3.6 *v* 12.1 ± 3.6 mm Hg; *P* = .002). Similar results were obtained, regarding BP parameters, when the groups with diastolic WCE above and below the median (15 mm Hg) were compared. In fact, clinic diastolic BP (100.1 ± 9.5 *v* 95 ± 10.9 mm Hg; *P* = .001) and SD from daytime diastolic BP (11.1 ± 2.8 *v* 9.8 ± 2.2 mm Hg; *P* = .001) were higher and mean daytime diastolic BP was lower (88.5 ± 9 *v* 90.9 ± 9.7; *P* = .025) in the subset with a greater diastolic ambulatory WCE. Furthermore, in this group a higher proportion of women were found (49 % *v* 36%; *P* = .026).

The percentage of patients in whom previous pharmacological treatment had been stopped was not different in the groups with high and low systolic (86% *v* 84%; *P* = NS) and diastolic (88% *v* 82%; *P* = NS) WCE.

The cardiac parameters of the four subsets of the study population are reported in Table 1. Left ventricular posterior wall and interventricular septum were thicker and LVMI was greater in the subsets with higher WCE. The significant association between the white coat phenomenon and LVM was confirmed in the whole study population by the results of multiple regression analysis where sex, age, duration of hypertension, body mass index (BMI), and daytime average BP were added to two distinct models, in which systolic and diastolic parameters were separately included.

In the first model comprising systolic values (R^2 = 25.3%), the independent predictors of LVMI were (in rank order of strength of association) daytime systolic BP (β = 0.34; *P* < .000001), systolic WCE (β = 0.19; *P* = .0004), age (β = 0.18; *P* = .0006), and BMI (β: 0.14; *P* = .009). In the second model including diastolic parameters (R^2 = 21.5%), the best predictor of LVMI was age (β = 0.29; *P* < .000001), followed by daytime diastolic BP (β = 0.23; *P* = .00004), diastolic WCE (β = 0.19; *P* = .0004), and BMI (β = 0.15; *P* = .005). The inclusion into these models of 24-h or nighttime average pressures, instead of

daytime values, did not significantly modify the results of multiple regression analysis.

Discussion

There is disagreement on the clinical and prognostic significance of WCE. Some investigators believe that this phenomenon is a benign conditioned response, that is not correlated to the extent of target organ damage.[5–10] Indeed, in the PIUMA study the magnitude of clinic ambulatory BP difference, taken as a measure of WCE, did not predict cardiovascular morbidity and mortality in subjects with essential hypertension, during an average follow-up of 4.2 years.[7] Discrepant conclusions have been reached in other longer longitudinal studies.[11,12] Alderman et al[11] observed greater risk of cardiovascular disease or myocardial infarction among hypertensives with higher diastolic BP reactivity, expressed as the difference between physician and nurse measurements. More recently, Strandberg and Salomaa[12] found that men characterized by a large WCE (defined by the physician–nurse BP difference) had a mortality rate 2.2 greater than those having a small WCE. In addition, Palatini et al[13] showed that in 1013 hypertensive outpatients the WCE, quantified as the clinic daytime ambulatory BP difference, was related to LVMI.

The findings of this latter study are in keeping with the results of our investigation. We found that the hypertensive subjects with the larger ambulatory WCE exhibited higher values of LVM when compared to the patients with lower WCE. The relationship of WCE with LVMI, independently of other potential confounders, was confirmed in multiple regression analyses, even after adjusting for age, duration of hypertension, sex, average daytime BP, and BMI.

Conflicting results of the literature about WCE may reflect, at least in part, different definitions of WCE and differences in the duration of the follow-up period and in the study population (general population versus hyperten-

sive subjects), as well as difference in the age of the participants. Moreover, in some studies the concept of WCE has been confused with that of white coat hypertension. Although the former is responsible for the existence of the latter, it should be emphasized that WCE and white coat hypertension are two separate entities.

The mechanisms of the adverse impact of WCE on the cardiovascular system remain uncertain. A widely held and attractive hypothesis is that this phenomenon represents a marker of the patient's tendency to hyperreact to any kind of stressful situations in everyday life with an exaggerated increase in BP and thus to display an enhanced BP variability throughout the day and night. This is in line with the greater short-term BP variability, as expressed by the standard deviation of daytime BP, which we found in patients with higher ambulatory WCE. It is also in agreement with, some experimental[14] and clinical studies[15] showing that sporadic elevations and variability of BP may not be innocuous. Stress-related BP fluctuations may act as a mechanical stimulus to the myocytes, activating protein synthesis, and hypertrophy. This process may be mediated by angiotensin II synthesis in cardiac tissue. Cardiac sympathetic nervous activity may also affect myocyte growth.

Because the cross-sectional nature of our study, we cannot exclude the possibility of an inverse causal relationship. An increased LVM may also contribute to an enhanced BP reactivity. For example, to the extent that LV hypertrophy impairs ventricular filling, it may trigger a compensatory pattern of accentuated peripheral vascular and noradrenergic responses, consistent with the present results. Furthermore, LV hypertrophy has been associated with a reduced baroreflex sensitivity that, in turn, may be responsible for a greater BP variability.

It is noteworthy that patients in whom treatment had been stopped may have influenced the results because of the persisting influence on LVM. The subjects previously treated were, however, equally distributed in the groups with high and low ambulatory WCE.

In conclusion, our results seem to suggest that in essential hypertensive patients ambulatory WCE, being associated with an increased left ventricular mass, may not be an innocent phenomenon.

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