The white coat effect is not associated with additional increase of target organ damage in true resistant hypertension


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ABSTRACT

Background and objective: White coat effect (WCE) (i.e., the difference between office blood pressure (OBP) and awake ambulatory blood pressure monitoring (ABPM)) may be present in hypertensive individuals. The relationship between occurrence of WCE and target organ damage (TOD) has not yet been assessed in true resistant hypertension (RHTN).

Patients and methods: RHTN patients were divided into two groups: RHTN with WCE (WCE, n = 66) and RHTN without WCE (non-WCE, n = 61). All patients were submitted to OBP measurement, ABPM, echocardiography and renal function evaluation in three visits.

Results: No differences were observed between the WCE and non-WCE groups regarding age, body mass index or gender. OBP were 169.8 ± 15.8/95.1 ± 14.0 (WCE) and 161.9 ± 9.0/90.1 ± 10.4 mmHg (non-WCE), ABPM = 143.0 ± 12.8/86.1 ± 9.9 (WCE) and 146.1 ± 13.6/85.1 ± 14.9 mmHg (non-WCE). No statistical differences were observed between WCE and non-WCE subgroups with respect to left ventricular mass index (LVM) (WCE = 131 ± 47; non-WCE = 125 ± 2.9 g/m²), creatinine clearance (WCE = 78 ± 4.7; non-WCE = 80 ± 3.6 ml/min/m²) and microalbuminuria (MA) (WCE = 44 ± 8.4; non-WCE = 49 ± 6.8 mg/g Cr).

Conclusions: This finding may suggest that WCE is not associated with additional increase of TOD in true RHTN subjects.

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El efecto de bata blanca sobre la presión arterial en pacientes con hipertensión resistente verdadera no se asocia con incremento adicional de lesiones en órganos diana

RESUMEN

Fundamento y objetivo: El efecto de bata blanca (EBB), es considerado cuando la diferencia entre la PAS/PAD medida en consulta médica y aquella obtenida por monitorización ambulatoria de la presión arterial (MAPA) y puede estar presente durante la consulta médica en pacientes con hipertensión arterial resistente (HTA-R). La relación entre la presencia del efecto bata blanca y daños en órganos diana aún no ha sido evaluada en individuos con HTA-R verdadera.

Pacientes y método: En este estudio, sesenta y seis pacientes con HTA-R verdadera presentaron EBB y otros 61 no lo hicieron. A todos los sujetos se les practicó una monitorización ambulatoria de la presión arterial durante 24 horas (MAPA). La afectación de órganos diana se determinó mediante la realización de ecocardiograma y evaluación de la función renal.

Resultados: Los valores de PAS y PAD en consulta médica fueron: 169.8 ± 15.8/95.1 ± 14.0 (pacientes con EBB) y 161.9 ± 9.0/90.1 ± 10.4 mmHg (pacientes sin EBB), respectivamente y mediante MAPA los valores promedio de PAS y PAD de 24 horas fueron: 143.0 ± 12.8/86.1 ± 9.9 (pacientes con EBB) y 146.1 ± 13.6/85.1 ± 14.0 mmHg (pacientes sin EBB), respectivamente. No se observaron diferencias significativas entre los pacientes con o sin EBB con respecto al índice de masa ventricular izquierda (con EBB = 131 ± 47; sin...
Introduction

Resistant hypertension (RHTN) is defined as being present when a therapeutic plan, including attention to lifestyle modification and the prescription of at least three antihypertensive agents of different classes in adequate doses, fails to lower systolic blood pressure (SBP) and diastolic blood pressure (DBP) sufficiently.\(^1\) In addition, patients whose blood pressure (BP) is controlled but who require four or more medications to reach the goal (of which is BP < 140/90 mmHg) should be considered resistant to treatment.\(^1\) ABPM is one of the valid methods to differentiate “isolated office RHTN” (or pseudo-RHTN) from “true RHTN”, providing higher prognostic value than OBP measurements in the evaluation of subjects with RHTN.\(^2\)

The BP measurement at the physician’s office can lead to a high OBP when compared with other out-of-clinic measurements, such as ABPM in hypertensive patients. This is known as the ‘WCE’; some theories have been put forward suggesting that it is significantly related to mental stress,\(^4\) emotional hyperresponsiveness or hyperreactive response on the part of the patient while being examined by the physician.\(^5\) Thus, WCE may be related to an alerting reaction mediated by the sympathetic nervous system that is associated with greater variability in BP.\(^4\) Moreover, sustained hypertension is associated with sympathetic predominance or decrease in parasympathetic activity, which has an influence on heart rate as well as BP.\(^6\) Some authors have found that WCE does not entail increased cardiovascular risk\(^7\) to hypertensive subjects, while it is associated with decreased hazard ratios for all-cause mortality.\(^8\)

The prognostic significance of WCE in RHTN patients is unclear.\(^6\) It is known that pseudo RHTN patients with manifesting WCE have less severe TOD when compared to those with true RHTN during ambulatory monitoring,\(^2\) meaning that the latter have a poorer prognosis than the former. However, no study has evaluated the influence of WCE on TOD in true RHTN. The aim of the present study was to assess whether WCE is associated with TOD in true RHTN.

Patients and methods

Patient population

We evaluated patients referred to the Resistant Hypertension Service of the University of Campinas for difficult-to-control hypertension. All individuals completed a medical history questionnaire and were submitted to physical examinations, electrocardiography and laboratory tests. Patients with secondary forms of hypertension, liver disease, coronary heart disease, strokes, peripheral vascular disease or any other major diseases, as well as smoking patients, were excluded. Patients were evaluated concerning adherence to treatment and underwent clinical optimization of antihypertensive therapy.\(^10\) Daytime ABPM (Spacelabs 90207, Spacelabs Inc., Redmond, WA, USA) is an auxiliary method to characterize RHTN and in our study it was used to exclude causes of pseudoresistance, including white coat hypertension (WCH). After a 6-month period (five to six visits), 127 patients were identified with true RHTN and included in the study. They were divided into two groups: RHTN with WCE (WCE, \(n = 66\)) and RHTN without WCE (non-WCE, \(n = 61\)). The mean duration of hypertension was 8.3 years in both groups. This study was approved by the Research Ethics Committee of the University of Campinas, São Paulo, Brazil and written informed consent was obtained from each patient before study participation.

Study design

Nonpharmacologic therapies were optimized, including dietary salt control, which were confirmed by the measurement of urinary sodium excretion (<100 mEq/24 h). All patients were submitted to OBP measurement, ABPM, echocardiography and renal function evaluation in three visits. WCE was defined as measurement of SBP > 20 mmHg and/or DBP > 10 mmHg, in the physician’s office, in comparison with daytime ABPM.\(^3\)

Measurements

Office blood pressure

With the patients in a seated position with the arm comfortably placed at heart level, BP level after resting for 5 min and OBP level were obtained according to American Heart Association.\(^10\) OBP was measured three times from each patient using a digital BP monitor (HEM-907 XL Omron). We used the mean value of the two last measurements as the final OBP level.

Ambulatory blood pressure monitoring

All participants underwent 24-h ABPM on a usual working day. They were instructed to act and work normally. The Spacelabs 90207 ambulatory blood pressure monitor (Spacelabs Inc., Redmon, WA) was used.\(^11\) The appropriate size cuff was placed around the nondominant arm. Readings were obtained automatically at 20-min intervals throughout the 24-h monitoring period. All participants of the study had at least 80% of the total measurements validated. Ambulatory blood pressure parameters included mean daytime SBP and DBP. All participants were instructed to describe their sleep period in a personal diary. The daytime and nighttime periods were defined individually for each record in accordance with bedtime reported by the patient. Also, WCH was extensively excluded as cause of pseudoresistance by ABPM, allowing that only true RHTN patients were included in this study.

Echocardiography

Measurements of left ventricle (LV) dimensions were performed according to the American Society of Echocardiography (ASE) recommendations, using a two-dimensional targeted M-mode echocardiography. LV mass was calculated by the recommended ASE formula.\(^12\) LV mass index (LVMi) was calculated dividing the LV mass by the body surface. Left ventricle hypertrophy (LVH) was defined as LV mass index > 115 g/m\(^2\) for men and >95 g/m\(^2\) for women. Echocardiography measurements were evaluated by two blinded investigators.

Laboratory assessment

Baseline blood samples for measurement of glycemia (mg/dl), total cholesterol (mg/dl), LDL cholesterol (mg/dl), triglycerides (mg/dl) and creatinine (mg/dl) were collected at 8 a.m. after overnight fasting, during which time individuals rested in the supine position for 8 h, followed by 1 h in an upright position in an
air-conditioned room (22–24 °C). Urinary sodium (mEq/24 h), creatinine clearance (ml/min/1.73 m²) and MA (mg/g Cr) rate were evaluated in 24-h sterile urine. The glomerular filtration rate was also calculated through the Cockcroft-Gault formula (140 – age × weight/creatinine × 72 for men and for women, multiplied by the correction factor of 0.85). The U-Alb level was measured as the albumin to creatinine excretion ratio (mg/g Cr) in the urine. MA was defined as U-Alb level between 30 and 300 mg/g Cr.

Statistical analysis

The Statistical Analysis System, version 8.02 (SAS Institute Inc., Cary, NC, USA), was used for all statistical analyses. The statistical analysis was performed descriptively and interpreted in an explorative way. Unpaired groups were compared using Mann–Whitney U test. Fischer exact test was used to determine whether certain group had significantly different proportion of a particular characteristic. A value of p < 0.05 indicated significance. Sample size was calculated to fit statistical power of 0.80 and two-tailed significance level of 0.05 for all studied variables. All values are expressed as mean ± SD (standard deviation).

Results

The general characteristics of the two RHTN subgroups are listed in Table 1. No differences were observed between the WCE and non-WCE groups regarding age, body mass index or gender.

As shown in Table 1, although a trend for higher office SBP (169.8 ± 15.8 mmHg) and DBP (95.1 ± 14.0 mmHg) values was observed in WCE group, the difference was not significant. However, the BP delta values (i.e., difference between physician’s office and daytime ABPM) registered were 28 ± 4 vs. 16 ± 3 mmHg for SBP and 16 ± 5 vs. 7 ± 2 mmHg for DBP in WCE and non-WCE groups, respectively (p < 0.05).

WCE patients received more anti-hypertensive drugs than non-WCE (5.2 ± 0.3 vs. 4.1 ± 0.2, respectively) (Table 2).

LVH was present in 75% of RHTN, with no significant differences between WCE and non-WCE groups. LVI was similar in both groups (131.7 ± 4.7 and 125.9 ± 2.9 g/m² in WCE and non-WCE patients, respectively [p = 0.19]).

Renal function measured by creatinine clearance was similar in both groups (78.5 ± 4.7 and 80.6 ± 3.6 ml min 1.73 m⁻² in WCE and non-WCE patients, respectively [p = 0.52]). MA was found in 45% of WCE and 50% non-WCE groups (p = 0.37) [44.6 ± 8.4 and 49.8 ± 6.8 mg/g Cr in WCE and non-WCE patients, respectively (p = 0.74)].

Discussion

In the present study, we compared LVH and renal dysfunction in two true RHTN subgroups: those with and without WCE. The main finding of this study is that TOD, evaluated by LVH, creatinine clearance and MA, were similar.

First of all, WCH should not be confounded with WCE. The WCH occurs when BP levels exceed 140/90 mmHg during office readings despite of normal levels when measured through ambulatory BP monitoring. Differently, the WCE is strictly characterized by an increase in BP with the presence of the health care professional and a higher OBP independently of the diagnosis of hypertension and normotension.

Increased TOD, including left ventricular mass and MA, have been compared among normotensives, white coat hypertensives, and sustained hypertensives. The prevalence of TOD is very high in resistant hypertensive subjects. In general, TOD in WCH is less than that in sustained hypertension, but the WCE is not associated with increased target organ involvement. Conversely, Hernandez-del Rey and colleagues have shown a higher proportion of patients with clinical TOD with true RHTN than those with pseudo-RHTN (WCHR). This difference may be explained by the fact that we included only RHTN patients characterized by increased BP levels in both ABPM and OBP. Thus, in these truly RHTN subjects, the presence of WCE was not associated with a higher degree of LVH or renal damage.

We found that LVH was present in 75% of RHTN, with no significant differences between WCE and non-WCE groups. It is well known that the extent of BP rise seems to be independently associated with LVH and left ventricular mass in hypertensive patients and long-term antihypertensive treatment may induce reductions in LVI and in the clinic-daytime differences for SBP.

Table 2

<table>
<thead>
<tr>
<th>Characteristic/variable</th>
<th>WCE (n = 66)</th>
<th>Non-WCE (n = 61)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total anti-HTN drugs</td>
<td>5.2 ± 0.3</td>
<td>4.1 ± 0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>96.1% (63)</td>
<td>92.5% (56)</td>
<td>0.24</td>
</tr>
<tr>
<td>Aldosterone receptor inhibitor</td>
<td>7.3% (5)</td>
<td>5.1% (3)</td>
<td>0.46</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>60.0% (39)</td>
<td>72.7% (44)</td>
<td>0.41</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>70.0% (47)</td>
<td>45.4% (27)</td>
<td>0.01</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>64.7% (43)</td>
<td>42.4% (26)</td>
<td>0.03</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>83.3% (55)</td>
<td>63.6% (39)</td>
<td>0.04</td>
</tr>
<tr>
<td>Centrally acting anti-hypertensive drug</td>
<td>16.6% (11)</td>
<td>13.6% (8)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Abbreviations: WCE: white coat effect patients. Values are means ± SD.

Table 1

<table>
<thead>
<tr>
<th>Baseline characteristics of true RH patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCE (n = 66)</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Clinical data</td>
</tr>
<tr>
<td>Female gender (%)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
</tr>
<tr>
<td>Daytime SBP (mmHg)</td>
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<tr>
<td>Daytime DBP (mmHg)</td>
</tr>
<tr>
<td>ΔSBP (mmHg)</td>
</tr>
<tr>
<td>ΔDBP (mmHg)</td>
</tr>
<tr>
<td>Laboratory parameters</td>
</tr>
<tr>
<td>Glycemia (mg dl⁻¹)</td>
</tr>
<tr>
<td>Cholesterol (mg dl⁻¹)</td>
</tr>
<tr>
<td>HDL-c (mg dl⁻¹)</td>
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<tr>
<td>LDL-c (mg dl⁻¹)</td>
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<tr>
<td>Triglycerides (mg dl⁻¹)</td>
</tr>
<tr>
<td>Creatinine (mg dl⁻¹)</td>
</tr>
<tr>
<td>Uric acid (mg dl⁻¹)</td>
</tr>
<tr>
<td>Sodium (mEq⁻¹)</td>
</tr>
<tr>
<td>Potassium (mEq⁻¹)</td>
</tr>
</tbody>
</table>

Abbreviations: n: number of patients; WCE: white coat effect; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL and HDL: low- and high-density lipoproteins, respectively; eGFR: estimated glomerular filtration rate; ΔSBP: difference between office systolic blood pressure and systolic daytime ABPM; ΔDBP: difference between office diastolic blood pressure and diastolic daytime ABPM. Values are means ± SD.
and DBP; however, no significant relationship between these two parameters was found when tested by multiple regression analysis. This study provided the first longitudinal evidence that clinic-daytime differences in BP have no substantial value in predicting the regression of TOD, such as LVH, which has prognostic relevance in RHTN. In addition, CV risk is more tightly correlated with out-of-office BP than clinic BP and among patients with RHTN. Twenty-four-hour ABPM is an independent predictor of CV morbidity and mortality, whereas OBP has been found to have no prognostic value. Therefore, based on our own and other authors’ findings, the occurrence of WCE is not responsible for higher LVH in RHTN. However, more research needs to be undertaken.

One interesting observation is that all the patients who took part in this study were overweight. Recently, we have demonstrated that body mass index is higher in uncontrolled RHTN subjects than in controlled ones, and also it is associated with greater LVH. Hypertensive patients with white coat phenomenon have greater sympathetic activation compared with normotensive subjects and hypertensive patients. The development of a particularly resistant form of hypertension in metabolic individuals can be partially attributed to vasocostriction from increased sympathetic activation. In general, the sympathetic predominance in hypertension is associated with deleterious effects on target organs, predicting the development of cardiovascular complications. Our results reinforce the relevance of obesity and a possible enhanced sympathetic activation in the determination of the increased cardiac mass index in both RHTN subgroups, but they do not seem to be related to the occurrence of white coat phenomena, which were not found associated with a higher degree of LVH.

MA is an important marker of TOD in patients with essential hypertension and is associated with higher rates of pressure. Furthermore, other authors showed that BP control appears to be fundamental for reducing MA. In our study, urine albumin excretion (UAE) was similar in both RHTN groups, suggesting that the occurrence of WCE did not aggravate MA in RHTN, as described by other authors for general hypertension.

MA correlates with OBP in RHTN, and it has a significantly higher prevalence in patients with true RHTN when compared with patients with pseudo-RHTN. Furthermore, these authors have shown MA and office SBP as the only two variables that independently predict the occurrence of true RHTN vs. WCE in pseudo-resistant hypertensive patients. RHTN is a common clinical problem in older (>75 years) and obese patients which is associated with an increasing incidence of diabetes and chronic kidney disease, and the prevalence of RHTN can be expected to increase. We found that both RHTN groups had a normal glomerular filtration rate (which is usually defined as >60 ml/min per 1.73 m²), and low MA probably because these patients were not as old and obese as those included in other studies.

In order to achieve an effective prevention of cardiovascular disease, RHTN patients require specific therapeutic interventions beyond reducing BP levels, such as the control of associated comorbidities and other metabolic dysfunctions. The WCE group had a higher prescription prevalence of angiotensin-converting enzyme inhibitors, angiotensin receptor blocker and calcium channel blocker than the non-WCE group. This difference might explain the greater protection against TOD in WCE patients. Also, long-term antihypertensive treatment may cause reductions in LVMI and WCE, but no significant relationship between these parameters was found when tested by multiple regression analysis. We also did not find this association for RHTN subjects as well as between reduced creatinine clearance or MA and occurrence of WCE.

Some limitations are important to note. First, this is a cross-sectional study and the potential implications of long-term crossovers between WCE and non-WCE groups do not allow us to extrapolate our results to prognostic outcomes. Second, since diabetes, smoking, dyslipidemia and all pseudo RHTN patients were excluded in order to minimize, as much as possible, any factors that could skew the results, a small number of RHTN patients were enrolled in the study. Finally, the possibility of having significant difference between the measured MA of both groups (type II statistical error) cannot be completely discarded since we had a statistical power below the desired value (0.73) for this particular variable analysis.

Although there is no doubt that both office and ambulatory BP still have an important role in the diagnosis and follow-up of RHTN patients and can be used to classify the lack of control in patients initially misdiagnosed with RHTN hypertension, we demonstrated that WCE is not associated with additional increase of TOD in true RHTN subjects. This finding suggests that future longitudinal studies need to be carried out to prove whether there is an incremental deleterious effect of WCE in TOD and which pathogenesis is involved in this effect in patients with true RHTN.

Competing interests
Leandro Boer-Martins is an employee of Novartis Biociências S.A. (Brazil).

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