White Coat Effect in Treated Versus Untreated Hypertensive Individuals: A Case-Control Study Using Ambulatory and Home Blood Pressure Monitoring

George S. Stergiou, Stamatis P. Efstathiou, Catherine K. Argyraki, Leonidas G. Roussias, and Theodore D. Mountokalakis

Background: Some studies have shown a significant white coat effect (WCE) (i.e., difference between clinic blood pressure [CBP] and awake ambulatory blood pressure [ABP]) to be present not only in untreated but also in treated hypertensive individuals. This study aims to assess 1) the prevalence and the magnitude of the WCE in treated versus untreated hypertensive persons, and 2) the usefulness of home blood pressure (HBP) versus ABP in the detection of this phenomenon.

Methods: A case-control study was conducted in 138 treated hypertensive patients and same number of sex- and age-matched untreated hypertensive subjects who had measurements of CBP (at least three visits), HBP, and ABP. Subjects with a WCE of >20/10 mm Hg (systolic/diastolic) were classified as clinic reactors.

Results: There was a trend for a larger WCE assessed by ABP monitoring in the untreated group (mean difference in systolic WCE, 1.8 ± 22.2 mm Hg, 95% CI −2.0 to 5.5; diastolic 1.8 ± 11.9 mm Hg, 95% CI −0.2 to 3.8) and for more untreated clinic reactors (27% untreated v 20% treated, odds ratio 1.5, 95% CI 0.9 to 2.7). The sensitivity, specificity, and positive and negative predictive values of HBP to detect clinic reactors correctly were 56%/62% (treated/untreated), 87%/84%, 52%/59%, and 89%/86%, respectively, with moderate agreement between HBP and ABP (κ 0.42/0.46).

Conclusions: In treated hypertensive patients, WCE seems to be reduced compared with that in untreated hypertensive persons but is not eliminated. In both untreated and treated hypertensive individuals HBP monitoring appears to be useful in the detection of the WCE, but it may not be appropriate as an alternative to the ABP method. Am J Hypertens 2004;17:124–128 © 2004 American Journal of Hypertension, Ltd.

Key Words: White coat effect, antihypertensive drug treatment, ambulatory blood pressure, home blood pressure.
magnitude of the WCE in treated versus untreated hypertensive individuals and 2) the usefulness of home BP (HBP) versus ambulatory BP (ABP) in the detection of this phenomenon.

Subjects and Methods
From 1995 to 2001, a total of 393 subjects with elevated BP attending the outpatient BP clinic have been assessed using a standard protocol of clinic, ambulatory, and home BP measurements. Treatment, if any, was continued unaltered throughout the protocol. Criteria for exclusion were repeated systolic BP >220 mm Hg or diastolic >120 mm Hg, as well as any change in antihypertensive medication or in treatment with drugs known to influence BP at least 4 weeks before and during the study. For the purpose of the present study, data from all the treated subjects of the above database were collected. Each treated subject was matched with a control subject. Control subjects were untreated individuals who were matched for age (same decade) and sex and who were consecutively obtained by searching the previously mentioned database of subjects.

BP Measurements
All subjects had their CBP, HBP, and ABP measurements within 4 weeks. Treated subjects were instructed to take all of their antihypertensive drugs in the morning just after arising from bed. Triplicate CBP measurements were performed at each visit in the morning (8 to 10 AM) after 5 min sitting rest and with at least 1 min between recordings using standard mercury sphygmomanometers (bladder size 15 × 35 cm or 18 × 38 cm where appropriate). The average of the second and third measurement of a single visit performed after patients had attended at least two previous visits at the outpatient’s clinic was used in the analysis.

The HBP was measured using validated automated electronic devices Omron HEM-705CP (Omron Healthcare GmbH, Hamburg, Germany; bladder size 12 × 23 cm or 14 × 28 cm where appropriate) with duplicate morning (6 to 10 AM, before drug intake if treated) and evening (6 to 10 PM) measurements after 5 min of being seated and with 1 min between recordings. A form was supplied to the patients to report home BP values. The average of measurements of days 2 to 6 was used in the analysis. ABP was measured using SpaceLabs 90207 devices on a workday before or after HBP monitoring (SpaceLabs Inc., Redmond, WA; bladder size 12 × 23 cm or 14 × 30 cm where appropriate; measurements at 20-min intervals for 24 h).

Analysis
The average awake, asleep, and 24-h ABP was calculated using individual patient-reported sleeping hours. Recordings with <30 valid measurements during the awake period and <10 during the asleep period were rejected. Patients providing <16 valid HBP readings or readings taken on <5 days were also excluded.

The WCE was defined as the difference between CBP and awake ABP, or the difference between CBP and HBP. A WCE of 20 mm Hg systolic or 10 mm Hg diastolic BP was regarded as clinically important (substantial WCE). Clinic reactors (subjects with a substantial WCE) were detected on the basis of systolic and/or diastolic BP.

Blood pressure values obtained using the three measurement techniques and the magnitude of the WCE in treated versus untreated subjects were compared by the Student paired t test. Pearson’s correlations were used for the assessment of the relation between the WCE detected using HBP and ABP. The proportions of clinic reactors among treated and untreated subjects were compared using the χ² test. The level of agreement between methods in the detection of clinic reactors was assessed using the κ statistic.

Results
Data from 276 subjects (138 treated and 138 untreated) were analyzed (mean age 55.9 ± 9.6 years, body mass index 28.1 ± 3.9 kg/m², prestudy visits 4.5 ± 4.1, 162 men). Untreated subjects had fewer prestudy clinic visits (2.6 ± 1.8 v 6.4 ± 4.8, P < .001) and higher BP values (average CBP 146.8 ± 17.9/93.6 ± 9.9 mm Hg [systolic/diastolic], HBP 141.3 ± 16.1/88.3 ± 10.1, awake ABP 141.6 ± 14.7/90.1 ± 10.8) compared with treated subjects (CBP 134.8 ± 16.0/83.8 ± 9.0, HBP 132.3 ± 14.2/81.8 ± 7.2, awake ABP 131.4 ± 12.1/82.1 ± 8.8) (P < .001 for all comparisons).

Based on ABP monitoring, there was a consistent trend for a greater magnitude of the WCE in the untreated group, which did not reach statistical significance (Table 1). There was also a nonsignificant trend for more untreated subjects to be considered as clinic reactors on the basis of the systolic and/or diastolic WCE (37 untreated [27%] v 27 treated [20%]; odds ratio 1.5, 95% CI 0.9 to 2.7).

Using HBP monitoring a larger WCE was detected in the untreated group, which reached statistical significance for diastolic BP (Table 1). A strong association was found between the WCE assessed using the HBP and the ABP method (r = 0.71/0.69 [systolic/diastolic] in untreated and r = 0.64/0.65 in treated subjects; P < .001 for all r values). The same proportion of clinic reactors (25%) was detected by HBP as by ABP monitoring. Again there was a trend for more clinic reactors to be detected in the untreated group that reached statistical significance for the systolic WCE (P < .05). Based on systolic and/or diastolic WCE, 39 untreated (28%) and 29 treated (21%) subjects were classified as clinic reactors using the HBP method (odds ratio 1.5, 95% CI 0.9 to 2.6).

The levels of agreement and the κ statistic between the two methods in the detection of clinic reactors between untreated and treated subjects are presented in Table 2. The sensitivity, specificity, and positive and negative pre-
dictive values of HBP to detect clinic reactors correctly were 56%/62% (treated/untreated), 87%/84%, 52%/59%, and 89%/86%, respectively, with moderate agreement between HBP and ABP (κ 0.42/0.46, with ABP used as the reference method).

Univariate correlations showed female sex (P < .01), age >65 years (P < .05) and systolic CBP >160 mm Hg (P < .01) to be significantly associated with the presence of a substantial WCE, whereas only female sex emerged as an independent predictor in multivariate analysis (P < .01).

Discussion

The presence of a significant white coat reaction in treated hypertensive individuals may have important implications on their management. However, no published study has provided a direct comparison of the prevalence of this phenomenon in treated versus untreated hypertensive individuals. This case-control study provides a direct comparison of the prevalence and the magnitude of the white coat phenomenon in treated versus untreated hypertensive persons. Two different approaches were used for the assessment of out-of-clinic BP and the detection of clinic reactors: the standard method with ABP monitoring and an alternative method using HBP monitoring.

In this study, there was a consistent trend for a smaller magnitude of WCE (approximately one half) in treated subjects. In fact, 95% CIs ruled out the possibility of a larger WCE in the treated group, whereas the opposite hypothesis could not be rejected. According to the 95% CI, the WCE in untreated individuals may be greater by 5.5/3.8 mm Hg (systolic/diastolic) compared with that in treated patients. These data suggest that although the WCE may be reduced, it is not eliminated as a result of antihypertensive treatment.

Given that the WCE was assessed in this study after at least three clinic visits had been performed, the observed difference in the number of prestudy visits between the two groups is expected to have negligible effect on the findings. Furthermore, the assessment of the WCE after at least three clinic visits and the rejection of the first of triple CBP measurements of each visit probably accounted for the attenuation of the WCE in the present study in both treated and untreated subjects as compared to previous reports.3,6

Table 1. White coat effect defined as the difference between clinic and awake ambulatory or home blood pressure in untreated and treated hypertensive subjects

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>White Coat Effect (mean ± SD)</th>
<th>Untreated-Treated Difference (mean ± SD)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBP–ABP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>5.2 ± 16.3</td>
<td>3.4 ± 15.0</td>
<td>1.8 ± 22.2</td>
<td>.36</td>
</tr>
<tr>
<td>Diastolic</td>
<td>3.5 ± 8.9</td>
<td>1.7 ± 8.3</td>
<td>1.8 ± 11.9</td>
<td>.07</td>
</tr>
<tr>
<td>CBP–HBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>5.5 ± 14.8</td>
<td>2.5 ± 13.0</td>
<td>3.0 ± 19.3</td>
<td>.07</td>
</tr>
<tr>
<td>Diastolic</td>
<td>5.3 ± 7.6</td>
<td>2.0 ± 7.5</td>
<td>3.3 ± 10.4</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ABP = awake ambulatory blood pressure; CBP = clinic blood pressure; HBP = home blood pressure.

Table 2. Classification of untreated and treated hypertensive subjects according to the presence of a white coat effect detected using ambulatory or home blood pressure monitoring

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>ABP–Yes HBP–Yes</th>
<th>ABP–No HBP–No</th>
<th>ABP–Yes HBP–No</th>
<th>ABP–No HBP–Yes</th>
<th>κ (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>9 (6%)</td>
<td>106 (77%)</td>
<td>12 (9%)</td>
<td>11 (8%)</td>
<td>0.34 (0.11)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>18 (13%)</td>
<td>95 (69%)</td>
<td>13 (9%)</td>
<td>12 (9%)</td>
<td>0.48 (0.09)</td>
</tr>
<tr>
<td>Systolic and/or diastolic</td>
<td>23 (17%)</td>
<td>85 (61%)</td>
<td>14 (10%)</td>
<td>16 (12%)</td>
<td>0.46 (0.09)</td>
</tr>
<tr>
<td>Agreement</td>
<td>78–83†</td>
<td>Disagreement 17–22†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>7 (5%)</td>
<td>115 (84%)</td>
<td>10 (7%)</td>
<td>6 (4%)</td>
<td>0.40 (0.12)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>12 (9%)</td>
<td>109 (79%)</td>
<td>6 (4%)</td>
<td>11 (8%)</td>
<td>0.51 (0.10)</td>
</tr>
<tr>
<td>Systolic and/or diastolic</td>
<td>15 (11%)</td>
<td>97 (70%)</td>
<td>12 (9%)</td>
<td>14 (10%)</td>
<td>0.42 (0.10)</td>
</tr>
<tr>
<td>Agreement</td>
<td>81–89†</td>
<td>Disagreement 11–19†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yes/no indicates presence/absence of a substantial white coat effect.
* All differences between untreated and treated subjects are nonsignificant.
† Between the ABP and the HBP method in the detection of subjects with a substantial white coat effect.
Abbreviations as in Table 1.
It should be stressed that in treated hypertensive patients the magnitude of the WCE may be affected by the time of BP measurement in the clinic or at home. In the present study, CBP was taken approximately 3 h after drug intake (that is, before the peak effect of the drugs), whereas morning and evening HBP represents the trough effect measured 24 h after drug intake and the plateau effect measured approximately 12 h after drug intake, respectively. Therefore, it could be argued that the difference in the magnitude of the WCE between untreated and treated hypertensive individuals might have been smaller had office measurements been performed at trough.

A reduction of the WCE with treatment has also been shown in a recent review of antihypertensive drug trials that provided data on the magnitude of the WCE before and after treatment in the same patients. However, the placebo effect and the time effect (regression to the mean) may account for the greater reduction of CBP than ABP in these studies, thereby giving the impression that the WCE is reduced by drug treatment.

In agreement with previous reports, the prevalence of a substantial WCE assessed by ABP monitoring in treated hypertensive individuals (20%) did not differ from that in untreated persons (27%) in the present study. However, given that the 95% CI did not exclude the possibility of the prevalence of treated clinic reactors being one half that of untreated ones, it could be argued that analysis of a larger sample may yield a significantly lower prevalence of clinical reactors in treated subjects.

There is some evidence suggesting that HBP monitoring may be useful in the assessment of the WCE. In the present study, HBP monitoring allowed evaluation of the WCE with greater precision than did ABP monitoring (lower SD of the WCE in both treated and untreated subjects; Table 1). Interestingly, HBP monitoring detected a greater difference in the magnitude of the WCE between treated and untreated subjects than the ABP method, with a narrower CI that reached statistical significance for diastolic BP (Table 1). In addition, the proportion of clinic reactors detected in treated and untreated subjects using HBP was similar to that using ABP.

Although we found relatively strong correlations between the WCE assessed using ABP and HBP in both treated and untreated hypertensive subjects, disagreement between methods in the diagnosis of clinic reactors was observed in up to 20% of subjects (Table 2). This discordance may be attributed to inherent limitations of the methods such as their imperfect reproducibility, as well as to inherent differences between them regarding the standardization of the measurements conditions.

The diagnostic characteristics of HBP monitoring (moderate sensitivity and positive predictive value but higher specificity and negative predictive value) in the detection of clinic reactors among both untreated and treated hypertensive persons in the present study suggest that this method is more appropriate to be used as a screening than a diagnostic test. These data are in accordance with the strategy proposed in 1990 by Pickering, which has been endorsed by an Ad Hoc Panel of the American Society of Hypertension and by several other investigators, suggesting that HBP monitoring should not replace ABP in diagnosis of the white coat phenomenon, but, rather, that its use should be restricted to screening purposes.

In conclusion, these data suggest that in treated hypertensive individuals the WCE tends to be reduced but is not eliminated. Moreover, HBP monitoring appears to be useful in the detection of the white coat phenomenon in both treated and untreated individuals, but it may not be appropriate as an alternative to the ABP method.

References

