White-Coat Resistant Hypertension
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The aim of this study was to evaluate whether sustained hypertensives with high clinic blood pressure, despite multiple drug treatment, show a true resistant hypertension or a “white-coat effect,” and whether the pretreatment white-coat effect is maintained despite pharmacological therapy. The occurrence of resistant hypertension was determined in 250 consecutive essential hypertensives who had had an ambulatory blood pressure monitoring before treatment assignment. Twenty-seven of 250 hypertensives with persistently high clinic blood pressure despite 3 months of adequate pharmacological therapy underwent further ambulatory blood pressure monitoring. Using our internal standards, seven patients had a true resistant hypertension whereas 20 subjects showed a large white-coat effect (white-coat resistant hypertension), ie, high clinic blood pressure (>140/90) but “normal” ambulatory daytime (<139/90 mm Hg) and 24 h (135/85 mm Hg) blood pressure. Using other cutoff points for ambulatory blood pressure, 134/90 and 135/85 mm Hg for daytime blood pressure, 10 and 13 patients, respectively, were reclassified as true resistant hypertensives and 17 and 14, respectively, were white-coat resistant hypertensives. Interestingly, in white-coat resistant hypertensives the large differences between clinic and ambulatory daytime blood pressure (white-coat effect), recorded before treatment assignment, were not affected by drugs and remained constant over time. Left ventricular mass index in white-coat resistant hypertensives was significantly lower than in truly resistant hypertensives, suggesting that prognosis could differ between these groups. In this study, using either our internal standards or some other cutoffs reported in the literature, the white-coat phenomenon was an important cause of resistant hypertension. The use of ambulatory blood pressure monitoring in these patients may avoid misdiagnosis of resistant hypertension, unnecessary overtreatment, and expensive procedures to look for possible secondary hypertension. Am J Hypertens 1997;10:1302–1307 © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: White-coat effect, ambulatory blood pressure monitoring, resistant hypertension.
occurrence of resistant hypertension (white-coat resistant hypertension) has not yet been clearly evaluated. Moreover, in previous studies, patients with white-coat hypertension, ie, high clinic blood pressure but “normal” ambulatory blood pressure in the absence of drug treatment, were not clearly differentiated from true hypertensives with a white-coat effect. Ambulatory blood pressure monitoring, performed before and after drug treatment, is the only method to differentiate white-coat resistant hypertensives from patients with a true drug-resistant hypertension or from subjects with white-coat hypertension.

The aim of this study was to evaluate whether sustained hypertensives with high clinic blood pressure despite multiple drug treatment show a resistant hypertension or a white-coat effect, and whether the pretreatment white-coat effect is maintained despite treatment.

METHODS

Patients and Study Design We studied 27 subjects (14 men and 13 women, age 56 ± 11 years) with a previous diagnosis of true hypertension confirmed by ambulatory blood pressure monitoring, who had persistently elevated clinic blood pressure (>140/90 mm Hg) despite being on a rational triple drug regimen for at least 3 months. These patients underwent a further ambulatory blood pressure monitoring to confirm the clinical diagnosis of resistant hypertension. They represented the 11% of 250 sustained hypertensives who were consecutively submitted to ambulatory blood pressure monitoring and were regularly followed by our secondary hypertension referral center. Patients referred to our center for suspected resistant hypertension who had not been submitted to ambulatory blood pressure monitoring before treatment assignment, and those found to have secondary hypertension and white coat hypertension, were excluded from the study. Only antihypertensive medications were being taken at the time of the study. All participants read and signed an informed consent.

Measurements Office Blood Pressure Clinic systolic and diastolic blood pressure recordings were performed on the same arm, with the patient sitting after 10 min quiet rest, according to a standard technique. Phase V was used to determine diastolic blood pressure. Measurements were performed in triplicate and the average value was used as the blood pressure for the visit. Resistant hypertension was defined as clinic blood pressure > 140/90 mm Hg, despite a triple drug regimen, in at least 3 visits (1 week apart). In patients with resistant hypertension the “Osler maneuver” was used to differentiate true hypertensives from those with falsely elevated blood pressure because of an excessive stiffness of the large brachial arteries (pseudohypertension). Ambulatory Blood Pressure Monitoring Ambulatory monitoring was performed with a portable noninvasive recorder (SpaceLabs 90207, Redmond, WA) on a day of typical activity after a clinic visit. Ambulatory blood pressure readings were obtained automatically at 15 min intervals from 6 AM to midnight, and at 30 min intervals from midnight to 6 AM. Each time a reading was taken, subjects were instructed to remain motionless and to record their activity on a diary sheet. On completion of ambulatory blood pressure monitoring the data were analyzed by computer, using a program designed to perform editing and interval statistics. All patients included in the study had recordings of good technical quality. The following ambulatory blood pressure monitoring parameters were evaluated: average daytime (awake period) systolic and diastolic blood pressure; average nighttime (sleep period) systolic and diastolic blood pressure; and average 24 h systolic and diastolic blood pressure. White-coat resistant hypertension was defined as high clinic blood pressure, despite triple treatment for at least 3 months, but “normal” ambulatory daytime and 24 h blood pressure. There is no general agreement concerning the normal limits of ambulatory blood pressure values, and different upper limits of normalcy have been used in previous studies. Thus, rather than using a previously reported cut-off point and in light of possible influence of geographical location on blood pressure, we have chosen the blood pressure values representing the upper limits (mean ± 2 SD) of a clinically normotensive population coming from our geographical area (Chieti, Abruzzo, Italy). The resulting upper limits for average 24 h and average daytime ambulatory blood pressure were 135/85 and 139/90 mm Hg, respectively. Patients were also reclassified according to different upper limits of ambulatory blood pressure.

Echocardiographic Study Echocardiographic examination was performed using a Hewlett-Packard 77030A (Andover, MA) ultrasound imaging system equipped with a 2.5 or 3.5 MHz transducer. Interventricular septum, posterior wall, and left ventricular dimension at the end of diastole were measured according to the American Society of Echocardiography recommendations. Left ventricular mass was calculated by the formula introduced by Devereux et al on the basis of necropsy validation studies. The left ventricular mass index (LVMi) was calculated by dividing the left ventricular mass by body surface area.

Medication Adherence Assessment All subjects were interviewed to collect information about nutritional history, smoking habit, and other relevant life-
Table 1: Clinical Characteristics and Drug Therapy of Patients with Resistant Hypertension (RH) and White-Coat Resistant Hypertension (WC-RH)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RH</th>
<th>WC-RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Men/women (n/n)</td>
<td>4/3</td>
<td>10/10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 12</td>
<td>59 ± 9*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 3</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/day)</td>
<td>90 ± 15</td>
<td>95 ± 11</td>
</tr>
<tr>
<td>Alcohol overconsumption (n)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Smokers (n)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>H + A + N (n)</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>H + E + N or V (n)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>H + N + C (n)</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

H, hydrochlorothiazide (25 mg); A, atenolol (100 mg); N, nifedipine GITS (90 mg); E, enalapril (20 to 40 mg); V, long-acting verapamil (240 or 360 mg); C, clonidine patch (0.2 mg).

*p < .03.

style factors. A comprehensive questionnaire and interview were used to evaluate the patient’s adherence to the drug regimen as well as the adequacy and tolerability of the antihypertensive therapy. Items included side effects experienced, reasons for not fulfilling prescriptions, difficulty in swallowing pills or opening medication containers, and medication taking behavior, such as taking drugs on the day of clinic visit or discontinuing drugs without physician consent.

Statistical Analysis Standard descriptive statistics, unpaired and paired Student’s t tests, and χ² tests were performed, where appropriate.18 Values are reported as means ± SD. The P < .05 level of significance was adopted for all tests.

RESULTS

The ambulatory blood pressure monitoring showed that only seven out of 27 patients (26%) had a truly resistant hypertension, whereas 20 patients (74%) presented a white-coat resistant hypertension. Subjects with resistant hypertension represented 2.8% of the original population of 250 consecutive untreated essential hypertensives. The cause of resistant hypertension was suboptimal therapy in one patient (patient did not increase drug dosage as prescribed by the physician), noncompliance in three patients (patients reported to not always take all the drugs), and undetermined in three patients. Recently, Alderman et al restricted the diagnosis of resistance only to patients adherent to medication.3 In our study, if we eliminate one patient with suboptimal treatment and three with noncompliance, the exact prevalence of true resistant hypertension is reduced from 2.8% to 1.2%. In all patients with resistant hypertension the “Osler maneuver” proved negative. There was no significant difference in sex distribution, body mass index, sodium intake (evaluated by urinary sodium excretion), alcohol intake, smoking habits, prevalence of diabetes mellitus, and medication regimens (Table 1) between the two groups. Patients with a white-coat resistant hypertension were older (P < .03) than those with true resistant hypertension. There was no difference in clinic blood pressure between the two groups (Table 2). Ambulatory blood pressures were significantly higher in patients with resistant hypertension than in those with white-coat effect (Table 2). Clinic blood pressure was significantly higher than daytime ambulatory blood pressure in patients with white-coat resistant hypertension (149 ± 4/97 ± 2 v 127 ± 7/78 ± 5 mm Hg, P < .0001), whereas no significant difference was present between clinic and ambulatory daytime blood pressure in the group with true resistant hypertension. The difference between clinic and daytime systolic and diastolic blood pressure, recorded before treatment assignment, was significantly higher in the white-coat resistant group when compared with that in a group of 20 age-, sex-, and weight-matched responders to antihypertensive therapy (20 ± 3/18 ± 2 v 7 ± 2/5 ± 2 mm Hg, P < .0001) and to truly resistant hypertensives (20 ± 3/18 ± 2 v 5 ± 2/3 ± 2 mm Hg, P < .0001). Noteworthy, in white-coat resistant hypertensives, despite a significant reduction in systolic and diastolic blood pressure, the value of this difference was not modified by the drug treatment (20 ± 2/18 ± 2 v 21 ± 3/18 ± 3 mm Hg, before versus after treatment, respectively; P = NS), showing very

Table 2: Clinic and Ambulatory Blood Pressure Values in Seven Patients with Resistant Hypertension (RH) and 20 Patients with White-Coat Resistant Hypertension (WC-RH) Treated with Multiple Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>RH</th>
<th>WC-RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic systolic BP (mm Hg)</td>
<td>151 ± 7</td>
<td>149 ± 4</td>
</tr>
<tr>
<td>Clinic diastolic BP (mm Hg)</td>
<td>98 ± 3</td>
<td>97 ± 2</td>
</tr>
<tr>
<td>24 h systolic BP (mm Hg)</td>
<td>143 ± 6</td>
<td>121 ± 10*</td>
</tr>
<tr>
<td>24 h diastolic BP (mm Hg)</td>
<td>93 ± 2</td>
<td>75 ± 5*</td>
</tr>
<tr>
<td>Daytime systolic BP (mm Hg)</td>
<td>148 ± 9</td>
<td>127 ± 7*</td>
</tr>
<tr>
<td>Daytime diastolic BP (mm Hg)</td>
<td>97 ± 4</td>
<td>78 ± 5*</td>
</tr>
<tr>
<td>Nighttime systolic BP (mm Hg)</td>
<td>131 ± 7</td>
<td>111 ± 11*</td>
</tr>
<tr>
<td>Nighttime diastolic BP (mm Hg)</td>
<td>83 ± 3</td>
<td>70 ± 7*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

BP, blood pressure.

*p < .001.
low coefficients of variation estimated on an individual basis (5.2% ± 1.5%, mean ± SD).

Left ventricular mass index was significantly higher in patients with resistant hypertension than in those with white-coat resistant hypertension (150 ± 9 vs 126 ± 10 g/m², P < .0001). Moreover, left ventricular mass index was not significantly different between white-coat resistant hypertensives and 20 age-, sex-, and weight-matched responder hypertensives (126 ± 10 vs 125 ± 10 g/m², P = NS).

In the white-coat resistant hypertensive group, drug therapy was reduced in 6 patients because of low ambulatory blood pressure levels and symptoms suggestive of hypotension.

When our patients were reclassified according to the cutoff points at first suggested by Pickering et al (134/90 mm Hg for daytime blood pressure), three white-coat resistant hypertensives were reclassified as true resistant hypertensives for systolic blood pressure (10 true resistant and 17 white-coat resistant hypertensive patients). When more restrictive criteria were used (135/85 mm Hg for daytime blood pressure), as suggested by Pickering, six white-coat resistant hypertensives were reclassified as true resistant hypertensives (13 true resistant and 14 white-coat resistant hypertensive patients).

**DISCUSSION**

Resistant hypertension does not represent an uncommon clinical problem and it may depend on different factors. It has recently been reported that some treated hypertensives show a white-coat effect that causes an overestimation of their blood pressure and underestimates the response to pharmacological treatment. This phenomenon is distinct from white-coat hypertension, that is, high clinic blood pressure but normal pressure at other times in untreated subjects. In our study, only seven of 27 patients (26%) with high clinic blood pressure despite triple therapy showed resistant hypertension, whereas the remaining (74%) presented a large white-coat effect in clinic and normal ambulatory blood pressure, that is, white-coat resistant hypertension. Thus, our data seem to demonstrate that, when secondary and white-coat hypertension have been excluded and volume overload is not present, a large white-coat phenomenon represents an important cause of “apparently” resistant hypertension. Moreover, its presence in untreated hypertensives may represent a predicting factor of a future false resistance to pharmacological treatment. In contrast with our findings, Yakovlevitich and Black reported a very low prevalence of “office resistance.” In fact, suboptimal therapy, previously undiagnosed secondary hypertension, and noncompliance were the most common causes of apparently resistant hypertension in their patients. However, they used different selection criteria and did not systematically perform ambulatory blood pressure monitoring to rule out the presence of a white-coat effect in all patients suspected to have resistant hypertension.

In a recent study Mejia et al, who performed an intraarterial monitoring in 15 subjects with suspected resistant hypertension, reported that only eight patients had a true resistance, whereas seven showed high clinic blood pressure but normal mean intraarterial blood pressure. Four of these seven subjects (27%) had “office resistance,” whereas in the other cases the cause of the resistance was represented by pseudohypertension or “cuff-inflation” hypertension. This lower prevalence of white-coat resistant hypertension may depend on the fact that their study was performed in a small number of highly selected patients, whereas our data come from a population of 250 consecutive untreated hypertensives.

In our study, because we have used non-invasive ambulatory monitoring, it is not possible to exclude completely the possibility that pseudohypertension or “cuff-inflation” hypertension may have contributed in determining resistant hypertension in our patients. Pseudohypertension is generally associated with a positive response to the Osler maneuver. The relatively young age of our patients with resistant hypertension (Table 1) and their negative response to the Osler maneuver seem to exclude the presence of pseudohypertension. Mejia et al have recently reported that “cuff inflation hypertension,” that is, a marked rise of intraarterial blood pressure occurring during cuff inflation, may represent a possible cause of pseudoresistance. Ambulatory blood pressure monitoring, as previously mentioned, cannot exclude the possibility that some of our patients resistant to treatment (that is, the three patients in which the cause of resistance was undetermined) had a “cuff-inflation hypertension”; nonetheless this phenomenon does not influence the high prevalence of white-coat resistant hypertension found in our study.

It is important to outline that ambulatory blood pressure decreased significantly in patients with a large white-coat effect (Table 2), and in some cases we were forced to reduce antihypertensive treatment because of an excessive fall in blood pressure. Thus, in white-coat resistant hypertensives, ambulatory blood pressure monitoring represents an important tool to check treatment efficacy to avoid overtreatment.

The differences between clinic and daytime blood pressure recorded before treatment in white-coat resistant hypertensives were significantly higher than
those found in truly resistant and in a well matched group of sustained hypertensives who responded to the therapy. Interestingly, in white-coat resistant hypertensives the treatment did not significantly influence this difference, which remained constant over time in each patient group, both for systolic and diastolic blood pressures.

It is known that clinic blood pressure is associated with cardiovascular risk; however, it has also been shown that ambulatory blood pressure is an independent predictor of prognosis. The prognostic significance of a large white-coat effect in true hypertensive patients is at present unknown. Prospective studies are needed to evaluate whether or not a large white-coat effect adds risk above that provided by ambulatory blood pressure. Verdecchia et al have recently reported that white-coat effect does not predict cardiovascular morbidity and mortality in hypertensive patients. Moreover, we have found that in the white-coat resistant hypertensives left ventricular mass index was significantly lower than in the truly resistant hypertensives and similar to that in the responders, potentially suggesting that these groups are characterized by different prognostic implications.

The present study has a limitation. We have used the cut-off points obtained by a normotensive population studied in our geographical area; however, we cannot exclude the possibility that these upper limits of normalcy could somehow overestimate the “true” upper limit of ambulatory blood pressure, thus leading to an overestimation of the prevalence of whitecoat resistant hypertension. In any case, by our using more restrictive criteria as well, half of our clinically resistant hypertensives showed a white-coat resistant hypertension, suggesting that this phenomenon is clinically relevant.

In conclusion, this study shows that many patients with apparently resistant hypertension show a large white-coat effect. Ambulatory blood pressure monitoring can reliably identify this subset of patients, thus avoiding unnecessary and possibly dangerous overtreatment or expensive and invasive procedures to look for possible secondary hypertension. Furthermore, we have shown that, in these patients, the large white-coat effect is not influenced by active pharmacological treatment.

REFERENCES


23. Koren MJ, Devereux RB, Casale PN, et al: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345–352.