Lack of Agreement Between Office and Ambulatory Blood Pressure Responses to Hydrochlorothiazide


Background: Differences between the antihypertensive responses to drug therapy measured by office blood pressure (OBP) and ambulatory blood pressure monitoring (ABPM) techniques have been noted but rarely analyzed. We studied whether the OBP and 24-h ABPM responses to hydrochlorothiazide differ and, if so, the relevance of these differences.

Methods: The OBP and ABPM responses to hydrochlorothiazide (25 mg/d, for 4 weeks) were measured in 228 subjects with essential hypertension, and mean responses were compared between methods using the Student paired t test. To assess variation in the agreement between OBP and ABPM responses among subjects, the limits of agreement were calculated as the mean difference between OBP and ABPM responses \( \pm 2 \) standard deviations.

Results: The mean systolic OBP response was 4.8 mm Hg greater than the response measured by ABPM (\(-14.3 \text{ v } -9.5 \text{ mm Hg, } P < .001\)), and the mean diastolic OBP response was 2.1 mm Hg greater than the response measured by ABPM \((-7.5 \text{ v } -5.5, P < .001\)). The limits of agreement between the OBP and ABPM responses ranged from \(-18.7 \text{ to } +28.2 \text{ mm Hg for systolic response and from } -12.9 \text{ to } +17.1 \text{ mm Hg for diastolic response. The systolic and diastolic OBP and ABPM responses were in opposite directions in } 22.8% \text{ and } 23.7\% \text{ of the subjects, respectively.}


Key Words: Ambulatory blood pressure monitoring, blood pressure determination, comparative study, hydrochlorothiazide.

Blood pressure (BP) responses, calculated as the difference between post-treatment and pretreatment BP levels, are commonly used as a measure of the effectiveness of antihypertensive drug therapy. Office BP (OBP), recorded by physicians or nurses using conventional sphygmomanometers, has been the standard method to measure BP and BP responses to antihypertensive interventions. However, the accuracy and precision of OBP have been questioned because of limiting factors such as BP variability and observer bias. In contrast to OBP, ambulatory BP monitoring (ABPM) records the BP in patients engaged in their normal activities throughout the whole day, is highly reproducible, is not subject to digit preference or observer bias, and avoids the so-called white coat effect.

Blood pressure levels measured by OBP are usually higher than ABPM readings. This observation has been extensively studied. In contrast, although it has been incidentally noted that BP responses measured by OBP are, on average, greater than those determined by 24-h ABPM, few studies have analyzed the differences for particular monotherapy or combination drug regimes or have assessed the range of variation among subjects in their OBP and ABPM responses. The objective of the present study was to assess whether the OBP and ABPM responses to a standard antihypertensive dose of a thiazide diuretic differ and, if so, the relevance of these differences.


From the Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic (JDF, GLS, STT), Rochester, Minnesota; Renal Division, Emory University (ABC), Atlanta, Georgia; and Human Genetics Center and Institute of Molecular Medicine, University of Texas–Houston Health Science Center (EB), Houston, Texas. This study was supported by U.S. Public Health Service grant R01-HL53330 and funds from the Mayo Foundation.

Address correspondence and reprint requests to Dr. Stephen T. Turner, Division of Hypertension, Department of Internal Medicine, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN; e-mail: turner.stephen@mayo.edu
Methods

The sample for the present study consisted of 228 subjects; 112 hypertensive non-Hispanic white adults from Rochester, MN (86 men and 26 women) and 116 hypertensive African-American adults from Atlanta, GA (59 men and 57 women). They were among 585 individuals who underwent monotherapy with hydrochlorothiazide as part of a study to identify predictors of BP response and agreed to have ABPM recordings. All procedures involving human subjects were approved by the institutional review boards of the Mayo Clinic and Emory University and were performed in accordance with institutional guidelines.

The study protocol has been described previously. In brief, subjects had to be in good health with BP of <180/<110 mm Hg and have no evidence of secondary hypertension, renal or liver dysfunction, heart disease, diabetes, gout, or sulfa allergy. Subjects had their previous antihypertensive medications withdrawn and were instructed in a diet designed to provide a standard sodium intake of 2 mmol/kg of lean body weight per day. They were seen every 2 weeks by the study nurse for BP measurements and were included in the study if, after discontinuing previous antihypertensive drug therapies for at least 4 but no more than 8 weeks, the diastolic BP was between 90 and 109 mm Hg and the systolic BP was <180 mm Hg. After the drug-free period, subjects began taking 25 mg of hydrochlorothiazide orally each day for 4 weeks.

At the end of the drug-free period before administration of hydrochlorothiazide (pretreatment), and after 4 weeks of hydrochlorothiazide (post-treatment), BP was measured in the dominant arm with an appropriate sized cuff using a random-zero sphygmomanometer (Hawksley and Sons, Ltd., West Sussex, England). An initial reading was obtained after 5 min of quiet rest in the sitting position. Two additional readings, taken at 2-min intervals, were recorded and their average was used as the OBP level for each visit. All readings were made between 7 and 9 AM at trough. After measurement of office BP, 24-h BP monitoring was initiated with the SpaceLabs model 90202 device (SpaceLabs, Redmond, WA). This device has been previously evaluated and was found to have accuracy similar to clinicians’ measurement of BP. In each subject, the device was attached and removed between 7 and 9 AM on consecutive days. Only those subjects who successfully completed ABPM recording both pre- and post-treatment were included in the study. In Rochester, MN, readings were obtained every 10 min and in Atlanta, GA, every 20 min. The mean (±SD) number of BPs recorded pre- and post-treatment were 124 ± 12.8 (range, 75 to 139) and 123 ± 9.8 (range, 92 to 140), respectively, in Rochester subjects; and 63 ± 4 (range, 44 to 70) and 62 ± 4.8 (range, 39 to 68) in Atlanta subjects. For each recording, the mean of all the readings was used as the ABPM in the analyses. The antihypertensive response was calculated as the difference between post-treatment and pretreatment BP levels for both the OBP and ABPM.

Consistent with current guidelines, the post-treatment systolic BP levels were considered “controlled” when the OBP was <140 mm Hg or when the ABPM was <135 mm Hg, and the diastolic BP levels were considered “controlled” when the OBP was <90 mm Hg or when the ABPM was <85 mm Hg. On the basis of these definitions, subjects were categorized into groups: those controlled by both the OBP and ABPM measures (ie, true normotensives), those not controlled by either the OBP or ABPM measure (ie, true hypertensives), those not controlled by OBP but controlled by ABPM (white coat hypertensives), and those controlled by OBP but not controlled by ABPM (masked hypertensives).

Descriptive characteristics for the participants are presented as mean ± SD. The OBP and ABPM means for pretreatment, post-treatment, and response were compared by Student paired t test. In addition, Pearson’s correlations were calculated between the OBP and ABPM values. To assess variation among subjects in the agreement between OBP and ABPM responses, the Bland-Altman limits of agreement were calculated as the mean difference between OBP and ABPM responses ± 2 standard deviations. Test statistics with P < .05 were considered statistically significant.

Results

Of the 228 subjects, 50.9% were African American, 36.4% were women, and 8.3% were smokers. Their mean age was 48.0 ± 7.2 years, and their mean body mass index (BMI) was 29.7 ± 4.9 kg/m². The mean duration of hypertension was 7.0 ± 7.4 years, and they had been previously on antihypertensive treatment for 5.7 ± 6.3 years. These characteristics did not differ significantly from the other 357 subjects in the parent study who were ineligible or did not agree to participate in this study, except for the smaller percentage of women (36.4% v 54.1%, P < .0001) and lower BMI (29.7 ± 4.9 v 32.3 ± 6.4, P < .0001).

The systolic and diastolic BPs measured by each method decreased significantly after 4 weeks of 25 mg of hydrochlorothiazide (P < .0001 for each response) (Table 1). The magnitudes of the systolic and diastolic mean responses measured by OBP were significantly greater than the ABPM responses (Table 1). Correlations between the two methods were significantly greater than zero but less than 1 for both the systolic and the diastolic responses (Table 1).

After 4 weeks of hydrochlorothiazide, systolic BP was controlled by both OBP and ABPM in 55.3% of subjects (Fig. 1, upper panel, left lower quadrant, A), and it was not controlled by either method in 18% of subjects (Fig. 1, upper panel, right upper quadrant, C). Systolic BP was con-
trolled when measured by OBP but not by ABPM in 23.2% of subjects (Fig. 1, upper panel, left upper quadrant, D), and it was controlled when measured by ABPM but not by OBP in 3.5% of subjects (Fig. 1, upper panel, right lower quadrant, B). The comparable percentages for diastolic BP control are presented in the lower panel of Fig. 1. In addition, 29.6% (53/179) and 38.5% (52/135) of the subjects, whose systolic and diastolic BPs were controlled by OBP, were not by ABPM (masked hypertensives, D in Fig. 1).

The mean difference between OBP and ABPM measures of systolic BP response was 4.8 ± 11.7 mm Hg, with limits of agreement from -18.7 to +28.2 mm Hg (Fig. 2). For the diastolic BP responses, the mean difference be-

### Table 1. Analysis of blood pressure after 25 mg of hydrochlorothiazide measured by office and ambulatory blood pressure monitoring

<table>
<thead>
<tr>
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<th>OBP (mean ± SD)</th>
<th>ABPM (mean ± SD)</th>
<th>Correlation (r)</th>
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<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
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<tr>
<td>Pretreatment</td>
<td>145.2 ± 14.2</td>
<td>143.9 ± 11.9 (NS)</td>
<td>0.67†</td>
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<tr>
<td>Post-treatment</td>
<td>131.0 ± 12.9</td>
<td>134.4 ± 12.6*</td>
<td>0.69†</td>
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<tr>
<td>Response</td>
<td>−14.3 ± 12.8</td>
<td>−9.5 ± 10.6*</td>
<td>0.51†</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>96.0 ± 5.2</td>
<td>91.1 ± 7.6*</td>
<td>0.43†</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>88.5 ± 8.1</td>
<td>85.7 ± 8.0*</td>
<td>0.59†</td>
</tr>
<tr>
<td>Response</td>
<td>−7.5 ± 7.9</td>
<td>−5.5 ± 6.2*</td>
<td>0.46†</td>
</tr>
</tbody>
</table>

ABPM = ambulatory blood pressure monitoring; OBP = office blood pressure.

* P < .001 OBP versus ABPM; † P < .0001.
between OBP and ABPM measures was $2.1 \pm 7.5$, with limits of agreement from $-12.9$ to $+17.1$ mm Hg (Fig. 2). Systolic BP decreased by both OBP and ABPM in 71.1% of subjects, and it increased by both measures in 61.1% of subjects. Systolic BP decreased by OBP but increased by ABPM in 13.6% of subjects, and it increased by OBP but decreased by ABPM in 9.2% of subjects (Fig. 3). The comparable percentages for the diastolic BP responses are shown in Fig. 3.

Discussion

The results of this study provide additional evidence that OBP overestimates the mean systolic and mean diastolic BP responses to hydrochlorothiazide compared to the responses measured by ABPM. Moreover, because of considerable variation among subjects in the magnitude and direction of BP responses measured by the two techniques, OBP provides an unreliable estimate of the ABPM response in individual subjects. Approximately one-third of the subjects in whom BP appeared to be controlled when measured by OBP were, in fact, not controlled when judged by ABPM. Conversely, approximately one-fifth of subjects in whom BP appeared to be uncontrolled when measured by OBP were, in fact, controlled by ABPM.

To our knowledge, only a few studies have addressed the differences in BP responses measured by different methods. In these reports, the responses measured by OBP were greater than those determined by self-recorded BP (at home) or by ABPM, as we observed. This observation appears to be consistent across study designs and the classes of antihypertensive drug studied, as noted in a recent meta-analysis of 44 studies of a variety of antihypertensive drugs in which the systolic and diastolic responses measured by ABPM averaged 36.5% and 36.8% less than the OBP responses. In one of the earlier studies of a β-blocker (bisoprolol) and a calcium channel blocker (nitrendipine), the calculated limits of agreement were from $-23.9$ to $+26.9$ mm Hg for the systolic OBP and ABPM responses and from $-17.0$ to $+22.6$ mm Hg for the diastolic OBP and ABPM responses. These estimates are similar to what we estimated for the OBP and ABPM responses to hydrochlorothiazide.

Although the present study, like previous studies, was not designed to explore mechanisms underlying the greater OBP than ABPM response, it can be hypothesized that the greater observed response reflects a combination of higher pretreatment OBP than ABPM and absence of a placebo effect on the post-treatment ABPM. The decline in OBP is due, in part, to a placebo effect, which has been attributed to regression toward the mean and habituation of the patient to both the clinic environment and the observer measuring BP. In contrast, the placebo effect is absent or minimal when BP is recorded using ABPM technique.

Limitations of our study relate to a possible selection bias, as not all subjects in the parent study participated in this study, the imposition of a standardized diet, a method of OBP measurement that differs from clinical practice, and different numbers of ABPM readings in Atlanta compared to Rochester. For the OBP, pre- and post-treatment levels, the systolic and diastolic responses, and the percentages of subjects in whom BP was controlled did not differ significantly between the 228 subjects included in this study and the 357 subjects in the parent study who did not participate (data not shown). The standardization of diet and the method used for measuring OBP would be expected to reduce the variability of OBP. If anything, this may have resulted in greater agreement between the OBP and ABPM responses than expected in usual practice. The greater number of ABPM readings in Rochester than Atlanta would be expected to increase precision of the BP levels measured pre- and post-treatment in Rochester. However, we observed that the limits of agreement for the systolic and diastolic BP responses were essentially the same for Atlanta and Rochester subjects (analyses not shown). In addition, the high frequency of measurement (every 10 min in almost half of the patients) might have produced sleep disturbances, which could result in an overestimation of the ABPM.
Our findings have important implications for patient care and clinical investigation. Because ABPM has been shown to be a better predictor of cardiovascular morbidity and mortality than OBP, it is important to recognize that OBP is a poor surrogate measure not only of ABPM level but also of response to antihypertensive drug therapy. A patient who appears to have responded well to a given antihypertensive drug as judged by post-treatment OBP, may be a nonresponder when judged by ABPM; conversely, a patient who does not appear to have responded by OBP, may actually be a good responder by ABPM. Moreover, as the magnitude and direction of the OBP response may differ considerably from and may be less reproducible than the ABPM response, studies designed to identify predictors of OBP (e.g., pharmacogenomics) may require larger sample sizes than those in which responses are measured by ABPM.

References