Prevalence and Persistence of Masked Hypertension in Treated Hypertensive Patients


Background: Masked hypertension (MH) is defined as a normal blood pressure in the physician’s office and an elevated blood pressure when measured out-of-office. The cause of MH may be termed the masked hypertension effect (MHE), and is not restricted to blood-pressure (BP) values around the thresholds for normal BP. We investigated the prevalence and persistence of MH and MHE in patients who were being treated for high BP and who had been followed for a period of 1 year.

Methods: One hundred and sixty-one treated hypertensive patients underwent office blood-pressure measurements (OBPMs) at seven visits and self-performed blood-pressure measurements (SBPMs) for 1 week before each visit over a period of 1 year. All measurements were performed with the same type of automatic device. At each visit, MH was determined according to the European Society of Hypertension definition (OBPM, <140/90 mm Hg; SBPM, ≥135 mm Hg or 85 mm Hg). In addition, we determined prevalences of MHE at 5/3 mm Hg (SBPM exceeds OBPM by 5 mm Hg systolic and 3 mm Hg diastolic), and MHE at 10/6 mm Hg (SBPM exceeds OBPM by 10 mm Hg systolic and 6 mm Hg diastolic), respectively.

Results: During the entire study, 50% of the patients had MH, and 40% had MHE at 5/3 mm Hg at least once. At four sequential OBPM visits, 2% consistently had MH, and 3% had MHE at 5/3 mm Hg or MHE at 10/6 mm Hg. The prevalence of MH increased with lower OBPM levels but remained rather constant for MHE at 5/3 mm Hg and MHE at 10/6 mm Hg. The persistence of MH and the MHE over time in individual patients was low.

Conclusions: We conclude that MH and MHE at 5/3 mm Hg and MHE at 10/6 mm Hg commonly occur in treated patients, but are not persistent phenomena and probably result from an accidentally low OBPM value on one particular occasion.

Key Words: Masked hypertension, reverse white-coat hypertension, white-coat normotension, self blood-pressure measurement, home blood-pressure measurement.
several studies assessed the occurrence of a phenomenon similar to MH among treated patients \(^7,^8\) or among both treated and untreated patients \(^9–^11\) and showed that such a discrepancy between office and out-of-office BP is also seen among treated patients \(^7–^11\). Because subjects with MH are at increased risk for developing cardiovascular events \(^7,^12,^13\), a reliable diagnosis is highly essential, whether patients are treated or not. In the present study, we investigated the prevalence and persistence of elevated self-measured BP values in combination with seemingly well-controlled office BP values among treated hypertensive patients. We sought to reveal whether elevated self-measured BP is a consistent phenomenon that is seen in multiple BP sessions, or if it is the result of an exceptionally low BP at the time of measurement because of intra-individual BP variability or inadequate performance of BP measurement. In addition, we investigated the persistence of the so-called masked hypertension effect (MHE) which is, in fact, the opposite of WCE. The rationale in doing so was based on the premise that MHE, contrary to MH, is not restricted to BP levels that are close to normal.

**Methods**

The patients included in the present analysis participated in the HOMERUS Trial, the design of which was described in detail elsewhere \(^14\). In brief, HOMERUS is a multicenter, prospective, randomized, double-blind trial with a parallel-group design. Both previously treated and untreated patients with essential hypertension qualified for inclusion, and were randomly allocated to either the self pressure (SP) group or to the office pressure (OP) group. If randomized to the SP group, the patient was instructed to start self-measurements of BP at home. In this group, stepwise antihypertensive treatment was guided by the results of SBPM. In the OP group, stepwise treatment was based on office readings. The prescribing physician was kept blind for the sake of randomization, and therefore was unaware whether the patient was treated according to OBPM or SBPM values. In accordance with current recommendations at the outset of this study, the target BP was set at 140 mm Hg systolic and 90 mm Hg diastolic, and the lower limit was set at 120 mm Hg systolic and 80 mm Hg diastolic for both groups. At entry into the study, any antihypertensive therapy was discontinued when the treating physician considered this to be safe, and patients entered a placebo run-in period of 4 weeks before the study treatment was initiated. If the treating physician considered an interruption of treatment to be too hazardous, the patient was switched immediately to trial medication. When BP was <140/90 mm Hg at the end of the run-in period, patients continued the study on placebo until changes were necessary. The duration of the trial was 1 year, during which time the OBPM and SBPM data were obtained at eight visits. Medication was adjusted according to a stepwise treatment schedule after each visit, and included an angiotension-converting enzyme (ACE) inhibitor (lisinopril), a diuretic (hydrochlorothiazide), and a calcium-channel blocker (amlodipine). A beta-blocker (atenolol) was administered when the ACE inhibitor could no longer be tolerated. All treatment decisions were made at the coordinating center, so that both the doctor and the patient were blinded to the medication. All patients gave informed consent, and the study was approved by the ethics committees of all participating centers before the inclusion of patients into the study.

For the present analysis, we considered only the group that performed SBPM, ie, 216 patients. These patients were followed for 1 year, during which time OBPM and SBPM data were obtained at eight visits. However, because the present study focused on blood-pressure measurements during antihypertensive treatment, we omitted the data from the first visit, which marked the end of the placebo period.

**Treatment Intensity**

The intensity of antihypertensive drug treatment was evaluated as follows: a weight of 0.5 was attributed to a daily dose of 10 mg of lisinopril, or 50 mg of atenolol, or 12.5 mg of hydrochlorothiazide. A daily dose of 20 mg lisinopril, or 100 mg atenolol, or 25 mg hydrochlorothiazide, or 5 mg of amlodipine was given a weight of 1. The intensity of combination therapy was calculated using the same weighing of drug doses.

**Blood-Pressure Measurements**

At every visit, three consecutive OBPMs were performed in the hospital or at the general practitioner’s clinic. Patients were asked not to take their pills on the day of BP measurement in the office. This was to prevent patients from being measured at the peak time of their dosing interval, which would lead to relatively low office BP values which may not have been representative of a patient’s average daytime BP. All patients also measured their own BP six times a day (three readings in the morning before drug intake, and three in the evening) for a 7-day period, before every visit. They were requested to register their self-measurements on a form, and to print out each measurement. The prevailing SBPM value was determined from the average of the 42 measurements. Both OBPM and SBPM were always performed on the nondominant arm, with the subject in sitting position, after at least 5 min of rest, using the same type of fully automated validated oscillometric device (Omron HEM-705 CP, Omron Healthcare Company Ltd., Japan) \(^15\). Ambulatory blood pressure monitoring (ABPM) was performed with a Spacelabs 90217 automatic device (Space Labs Medical, Inc., Redmond, WA), which passed the validation procedure \(^16\). Measurements were taken every 15 min between 7:00 AM and 11:00 PM, and every 30 min from 11:00 PM to 7:00 AM. The average daytime ABPM value was calculated from 9:00 AM to 9:00 PM on the first day, omitting the initial hour. \(^17\)
Laboratory Analyses

Blood was drawn from fasting patients for the determination of blood glucose, serum cholesterol (total and HDL cholesterol), and serum creatinine levels. Urinary (micro-)albumin concentrations were assessed from two consecutive 24-h urine collections. All microalbumin measurements were performed in the same laboratory.

Prevalences

At each visit, the number of patients with MH or of cases for whom SBPM was higher than OBPM were assessed. The measurement of MH followed the European Society of Hypertension (ESH) guidelines, which state that MH is present when OBPM values are <140 mm Hg systolic and <90 mm Hg diastolic, while the SBPM value is ≥135 mm Hg systolic or ≥85 mm Hg diastolic. The effect underlying MH was also studied in a quantitative sense, using two different definitions: (1) the SBPM value is 5 mm Hg systolic and 3 mm Hg diastolic higher than the OBPM value (MHE at 5/3 mm Hg), and (2) SBPM values exceed OBPM values by 10 mm Hg systolic and 6 mm Hg diastolic (MHE at 10/6 mm Hg). In addition, the prevalence and persistence of MH, of MHE at 5/3 mm Hg, and of MHE at 10/6 mm Hg were determined, using ABPM in addition to SBPM, at the end of the study.

Statistical Analyses

Correlations were calculated using linear regression. For determining differences in persistence and prevalence, we used chi square tests with Bonferroni correction for multiple comparisons. Differences in OBPM and SBPM values were assessed with a paired t test for normal distributions. Analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, IL). P < .05 was considered significant (two-sided).

Results

Of 216 patients with SBPM who were included in the trial, 19 did not complete the study because they withdrew their consent (n = 18) or had an adverse event (n = 1). Another 36 patients were excluded from the analysis because they were untreated at one or more visits (n = 12), or because they missed one follow-up visit or skipped one SBPM session before a visit (n = 24). These 55 patients did not differ from the remaining 161 patients, whose characteristics are presented in Table 1. On average, patients performed 42 ± 1 of 42 scheduled SBPMs. Eight patients received study treatment 2 weeks earlier than prescribed by the protocol, because the treating physician considered the withholding of medication irresponsible.

Blood pressure and heart-rate values for all seven visits are given in Table 2. Blood pressure fell with every visit, and at all visits, average SBPM values were significantly lower than the corresponding OBPM values (P < .001 for all).

Figure 1 shows the proportion of treated patients for each visit who were diagnosed with MH or had MHE at 5/3 mm Hg or MHE at 10/6 mm Hg. Whereas the prevalence of MH increased during the trial (when BP fell because of intensified treatment), it remained stable for both MHE at 5/3 mm Hg and MHE at 10/6 mm Hg. Additional analyses revealed that there were no significant differences for gender, age (<60 years and ≥60 years), and the presence or absence of left-ventricular hypertrophy. However, for all occasions of BP measurement together, there was a trend toward a higher percentage of MH, MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg in women than in men, although this did not reach statistical significance (18 v 14%, P = .09; 17 v 13%, P = .09; and 9 v 7%, P = .08, respectively).

Figure 2 shows the prevalences of patients who had MH only once or else more often during the seven measurement occasions. Over 50% of all patients were classified as manifesting MH at least once according to the ESH definition, but only half of them also had MH for a second time during the trial. Only a very small percentage of patients had MH for >5 visits, and in none of the subjects did MH persist for >6 visits. Similar trends were observed with respect to MHE at 5/3 mm Hg and MHE at 10/6 mm Hg.

Because there was little overlap in the occurrence of MH (24% on average), MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg (25% and 30% on average, respectively) between visits, it follows that most patients who manifested MH at one visit did not have the condition at the next visit (Fig. 3). Indeed, very few patients had MH,
MHE at 5/3 mm Hg, or MHE at 10/6 mm Hg for ≥4 consecutive visits.

Table 3 lists the prevalences of MH, MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg when these were based on either systolic or diastolic BP values only. The results are very similar to those based on the combination of systolic and diastolic pressure.

Figure 4 depicts the average percentage of patients with MH, MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg separated on the basis of drug intensity during the last half year of treatment, when patients had already been receiving medication for 6 months. Although patients with the lowest drug intensity (0.5) tended to have a lower prevalence of MHE at 5/3 mm Hg, or MHE at 10/6 mm Hg for ≥4 consecutive visits.

FIG. 1. Percentage of treated patients who were classified, per visit, as manifesting masked hypertension (squares); MHE at 5/3 mm Hg (triangles), ie, self blood-pressure measurement (SBPM) exceeds office blood-pressure measurement (OBPM) by 5 mm Hg systolic and 3 mm Hg diastolic; and MHE at 10/6 mm Hg (circles), ie, SBPM exceeds OBPM by 10 mm Hg systolic and 6 mm Hg diastolic. Straight line indicates regression line for masked hypertension (r = 0.76; P < .05). For MHE at 5/3 and MHE at 10/6, relationships were not statistically significant.

FIG. 2. Prevalence of treated patients with masked hypertension (MH), a masked hypertensive effect (MHE) at 5/3 (self blood-pressure measurement [SBPM] exceeds office blood-pressure measurement [OBPM] by 5 mm Hg systolic and 3 mm Hg diastolic), and MHE at 10/6 (SBPM exceeds OBPM by 10 mm Hg systolic and 6 mm Hg diastolic), based on blood-pressure measurements on seven occasions. The X-axis depicts total number of visits (not necessarily consecutively) during which the condition was found.
ence of MH, MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg compared with all other intensities, the differences were not statistically significant. The prevalence of MHE at 5/3 mm Hg and MHE at 10/6 mm Hg in patients with unchanged treatment showed that the percentages remained stable during the course of the study (10% and 6%, respectively, data not shown).

Finally, we found that the percentages of MH, MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg, based on daytime ABPM data at the end of the study, amounted to 12%, 10%, and 6%, respectively.

Discussion

Our findings show that at seven consecutive visits, more than half of all patients were classified at least once as exhibiting MH, and 40% had MHE at 5/3 mm Hg at least once. A small proportion of patients exhibited MH, MHE at 5/3 mm Hg, or MHE at 10/6 mm Hg on multiple occasions, but even then, not usually on consecutive visits. Only 2% of all patients had MH, 3% had MHE at 5/3 mm Hg, and 2% had MHE at 10/6 mm Hg on four consecutive visits. Although women tended to have higher percentages of MH, MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg than did men, the differences failed to reach statistical significance. The prevalence of the effect underlying MH also tends to be greater during intensified treatment, but again, this was not statistically significant.

Among patients receiving no changes in treatment, the percentage of patients with MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg, based on daytime ABPM data at the end of the study, amounted to 12%, 10%, and 6%, respectively.

Table 3. Prevalence of patients per visit with self-measurement values that are at least 5 or 10 mm Hg systolic or 3 or 6 mm Hg diastolic higher than corresponding office blood-pressure values

<table>
<thead>
<tr>
<th>Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBPM-SBPM</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

OBPM = office blood-pressure measurement; SBPM = self blood-pressure measurement; n = number of patients.
present study prescribed treatment according to a prespecified stepwise schedule, most patients received the same combination of antihypertensive drugs, and therefore this question could not be answered using the present data.

Although the ESH definition of MH is commonly accepted, it only detects patients with BP values around the upper limits of normality. However, patients who have marginally elevated BP in the office but substantially higher BP at home should probably be treated more aggressively, because even small increases in a patient’s usual pressure are associated with an increased risk of cardiovascular complications.21

Because we considered it important to detect all differences between OBPM and SBPM, we determined the prevalence of the effect underlying MH, and we adopted two definitions of the differences between SBPM and OBPM which we consider to be clinically relevant, ie, MHE at 5/3 mm Hg, and MHE at 10/6 mm Hg. Epidemiologic evidence supports the relevance of these values: each 5 mm Hg increment in systolic BP increases the risk of stroke by 18% to 30%, and the risk of all cardiovascular events by 9% to 18%.11,20 Even an increased diastolic BP of 5 to 6 mm Hg has shown to enhance the risk of stroke by 35% to 40%, to enhance the risk of coronary heart disease by 20% to 25%, and to increase the risk of all cardiovascular events by 12%,7,19,21,22

Another reason for using the present definitions is for validation of the BP device that we used in this study, the European Society of Hypertension and the British Hypertension Society allow an inaccuracy of up to 5 mm Hg.15 To allow for this inaccuracy, we used a “gray zone,” and decided that the systolic SBPM value had to be at least 5 mm Hg systolic higher than the OBPM value.

One may argue that the differences between an OBPM and SBPM of 5 mm Hg systolic and 3 mm Hg diastolic are small and thus irrelevant for diagnosis in an individual. However, it should be realized that SBPM values are regularly lower than OBPM values. In the present study, the average SBPM value was at least 6 mm Hg lower than the average OBPM value at any visit, which may imply that differences between SBPM and OBPM should be interpreted differently than the BP differences obtained by similar measurement techniques.

The prevalence of MH was higher with lower OBPM levels. However, the prevalences of MHE at 5/3 mm Hg and MHE at 10/6 mm Hg remained constant. Hence, there is some justification to use these differences because they are not only applicable at any BP level, but also provide more clinically relevant information about a patient’s BP status.

Masked hypertension recently became a topic of interest, and several studies addressed this issue in some detail. Cross-sectional studies showed huge differences in the prevalence of MH, varying from 8% in a general population to 49% in transiently hypertensive subjects.23 It is also seen in children and young adults (11%),24 and may be as common as white-coat hypertension.25 Patients with MH had degrees of target-organ damage26,27 and similar cardiovascular prognosis comparable to those of true hypertensive patients.7 This suggests that patients with masked and sustained hypertension are not fundamentally different from each other, but represent a different phenotypic expression of high BP.

A few studies evaluated the reliability of SBPM for detecting MH. For instance, Stergiou et al demonstrated that SBPM is as reliable as ABPM for diagnosing MH.9 According to Mallion et al, three measurements at two visits for OBPM, and three measurements in the morning and in the evening over 2 days for SBPM, are required for a reliable diagnosis of MH.28 However, none of these studies investigated whether MH persists after repeated testing.

In the interpretation of our results, some limitations should be taken into account. Data were collected from the HOMERUS Trial,14 which was designed for purposes other than those described here. Patients were treated on the basis of their SBPM results. This means that most patients with MH received intensified treatment, which may have prevented them from manifesting MH on the next occasion, since by then the SBPM values were usually reduced. On the other hand, OBPM values tended to be higher even after this intensification of treatment, suggesting that an accidentally low OBPM was a greater determinant of MHE.

During treatment, OBPM and SBPM were taken at different times during the dosing intervals of the prescribed antihypertensive drugs. Although patients were asked not to take their medication before OBPM was performed, this may have affected the results. In addition, our patients had mild to moderate hypertension, and thus our data cannot be extrapolated to other populations. Finally, in the present study, both OBPM and SBPM were performed with the same type of automatic device. This ruled out measurement errors due to different devices or observer bias as the cause of divergent results. However, this may also have reduced the differences between both types of measurement, and consequently may have led to overestimations of MH.

Because hypertension can hardly be considered as masked when patients are already being treated for that disease, one may argue that MH should not be investigated among patients who are diagnosed with clinically manifest hypertension. However, several studies noted that MH is frequently seen among treated patients,7–11,29 a finding which is confirmed by the present study. Physicians who are confronted with patients who exhibit MH may erroneously think that these patients are already on optimal treatment, which could lead to less effective surveillance of these patients.

Taking all our results together, the prevalence of MH can increase to almost 20% in treated hypertensive patients who have BP values around the threshold value of 140/90 mm Hg. The prevalence of MHE at 5/3 mm Hg amounts to about 12% at each visit. This indicates that
manifestations of MH, MHE at 5/3 mm Hg, or MHE at 10/6 mm Hg are not the exception in treated patients, and may even be a consequence of treatment. On the other hand, few patients exhibited MH, MHE at 5/3 mm Hg, or MHE at 10/6 mm Hg on multiple subsequent visits. Therefore, we conclude that these are not persistent phenomena, but are the result of an exceptionally low office BP value at time of measurement. Because several studies indicated that SBPM is more reliable than OBPM,30 we assume that MH is the result of an artifactual OBPM or a deviating OBPM as a consequence of a patient’s BP variability. Previously, we analyzed BP differences in the reverse direction, which produced the WCE.31 Interestingly, in that study, we found data regarding the prevalence and persistence of WCE that were very similar to data in the present study with respect to MH. Taken together, these results lend further support to the hypothesis that MH is not a separate clinical entity, but rather the result of random variability of measurements.

Conceivably, when using cutoff values (as in the case of MH), only small BP changes can lead to different diagnoses and interpretations in patients with BP values around these cutoff values. Therefore, we recommend the use of MHE in clinical practice. The MHE has a “gray zone,” such that small differences in BP do not immediately lead to different interpretations, and the effect underlying MH is not restricted to BP values around the threshold values for normal BP.

Because of the striking lack of consistency in both MH and MHE, patients who show these phenomena should not be treated as a special patient group. In addition, one wonders whether it is useful to search for these conditions in the first place. If, for any reason, SBPM has been performed and MH or the MHE has been found, we recommend performing OBPM and SBPM again after adjustment of treatment (insofar as patients are still hypertensive during part of the day). Only if the results remain contradictory (which will be the case in approximately 2% of the patients) is it justified to make a diagnosis of MH.

References


