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Detection of Masked Hypertension and the 'Mask Effect' in Patients With Well-Controlled Office Blood Pressure

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Background: Masked hypertension (MH) is characterized by its hidden nature and poor prognosis. However, it is not practical to routinely recommend home or ambulatory blood pressure monitoring (HBP or AMBP) to all patients with apparently well-controlled BP. The purpose of this study is to present, within the group of patients with well-controlled office BP (OBP), the clinical predictors of MH and to evaluate the gap (ie, the 'mask effect' (ME)) between OBP and HBP.

Methods and Results: BP was measured at the outpatient clinic and at home in 1,019 treated hypertensive patients. Candidate predictors for MH were analyzed within 511 patients with well-controlled OBP (45.6% men, 57.1±9.0 years). Among them, the prevalence of MH was 20.9% (n=107). In the multivariate-adjusted analysis, the risk of MH increased with high serum fasting blood glucose level (odds ratio (OR) 1.009, 95% confidence interval (CI): 1.001–1.018, P=0.020), higher systolic OBP (OR 1.075, 95%CI 1.045–1.106, P<0.001), higher diastolic OBP (OR 1.045, 95%CI 1.007–1.084, P=0.019) and the number of antihypertensive medications (OR 1.320, 95%CI 1.113–1.804, P=0.021). Furthermore, systolic HBP correlated well with systolic OBP (r=0.351, P<0.001) and with the degree of systolic ME (r=–0.672, P<0.001).

Conclusions: To recognize MH, it is practical to investigate those patients who are taking multiple antihypertensive drugs and have a high OBP with a high FBG level. The term "ME" identifies MH more appropriately than the term "negative white-coat effect". (*Circ J* 2011; **75:** 357–365)

Key Words: Blood pressure; Home monitoring; Masked hypertension; White-coat effect

The assessment of out-of-office blood pressure (BP), using either ambulatory or home BP monitoring, has enabled detection of masked hypertension (MH) and the "white-coat" hypertension (WCH) phenomena. Studies have shown that MH carries a similar cardiovascular risk to uncontrolled hypertension (UH).[1] Both home BP self-measurement (HBP) and ambulatory BP monitoring (ABPM) have been shown to be better correlated with target organ damage than conventional BP measurement in a clinic office.[2] Moreover, several studies have shown that either self-measured HBP or ABPM can predict cardiovascular mortality and morbidity more accurately than BP measurements at a clinic.[3–5] Even in a patient whose conventionally measured office BP (OBP) is normal, the self-measured HBP or ABPM value may still be high. In other words, UH can remain hidden until self-measurement of HBP or ABPM is performed.

The "white-coat" effect (WCE), which is usually defined as the difference between the OBP and HBP (or ABPM), is typically positive and present in the majority of hypertensive patients.[6] The term 'negative WCE' is used when the OBP minus HBP is a negative value. The magnitude of the nega-

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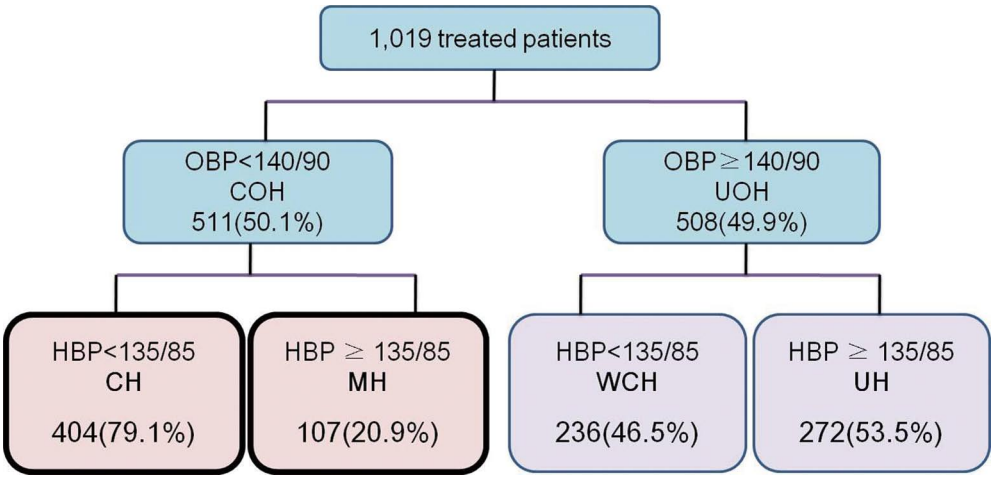

Figure 1. Patients classified by treatment status, and their office and home blood pressure values. OBP, office blood pressure; HBP, home blood pressure; COH, controlled office hypertension; UOH, uncontrolled office hypertension; CH, controlled hypertension; MH, masked hypertension; WCH, white-coat hypertension; UH, uncontrolled hypertension.

tive WCE well reflects the outcome of MH.[7] However, the majority of patients with MH have a negative WCE, which may have negative implications for them. In the case of MH, the reversed meaning of this term, as in the "mask effect" (ME), can seem illogical and confusing.

The characteristics, prevalence and outcome of WCH have been extensively investigated.[8,9] However, studies of MH have been limited to date. In recent years, MH has become a particular focus of attention because of its high prevalence, ranging from 7% to 45% in the general population,[10] and in part because of its poor cardiovascular prognosis.[11] Indeed, the cardiovascular risk of MH has been demonstrated to be the same as that linked to UH. Accordingly, it seems necessary to recognize MH within clinically controlled hypertensive patients and to treat it as UH. However, it is still uncertain whether MH is also common in patients referred to the outpatient clinic, or if it is associated with distinguishable clinical features within the cohort of patients with controlled office hypertension.[12]

The present investigation aimed to determine the clinical profile and predictors of MH and to evaluate the meaning of the ME ('negative WCE') in order to clarify its the clinical importance and implications.

Methods

Subjects and Clinical Data

The study included 1,019 (57±10 years, females 52%) consecutive hypertensive subjects who were recruited in 9 university hospitals in South Korea. The patients had been taking the same medications for more than 6 months. All BP measurements were done using the same device. Patients were classified into 4 groups according to both their OBP (≥140/90 mmHg) and their HBP (≥135/85 mmHg): (1) controlled hypertension (CH: normal OBP and HBP), (2) WCH (high OBP but normal HBP), (3) MH (normal OBP but high HBP), and (4) UH (high OBP and HBP). Controlled office hypertension (COH) included CH and MH, and uncontrolled office hypertension (UOH) included WCH and UH (Figure 1). The WCE was defined as OBP minus HBP, and the ME was defined as HBP minus OBP. The study protocol was approved by the institutional review board of each hospital.

A standardized questionnaire on familial, medical and social history was administered to each subject. Medical history was particularly aimed at identifying the complications of hypertension, as well as the presence of diabetes, dyslipidemia, family history of premature coronary heart disease (under 55 years of age for men and under 65 years for women), and accompanying target organ disease (ie, cardiac, cerebral, renal disease, and peripheral artery disease). The type and administration schedule of all medications were also recorded. Demographic data included age, sex, body weight, height, and body mass index (BMI).

Procedures

All patients underwent both OBP and HBP measurements. The OBP was measured by a physician using a mercury sphygmomanometer, with a cuff deflation rate of 2 mmHg/s. At each checkup visit, 2 measurements of OBP were performed consecutively while the patient was seated after resting for at least 2 min. UH based on the OBP was defined as systolic OBP ≥140 mmHg and/or diastolic OBP ≥90 mmHg.

Patients were asked to measure their seated BP once every morning within 1 h of waking, before taking antihypertensive drugs, and once every evening 1 h before going to bed, after more than 2 min of rest each time, as specified by the Japanese guidelines for HBP measurement.[13] They were asked to record the results over a 1-week period, and all measurements (≥10 measurements) were averaged. Physicians, nurses and patients used the same cuff oscillometric method with electronic arm-cuff devices (Omron HEM 747, Omron Healthcare Co Ltd, Kyoto, Japan). The mean of all measurements was calculated for each patient and used for the analysis. UH based on HBP (home hypertension) was defined as systolic HBP ≥135 mmHg and/or diastolic HBP ≥85 mmHg.

The following parameters were evaluated: systolic WCE (WCEsbp, the value of systolic OBP minus average HBP); corrected systolic WCE (coWCEsbp, the value of WCEsbp minus 5 mmHg); systolic ME (MEsbp, the value of systolic

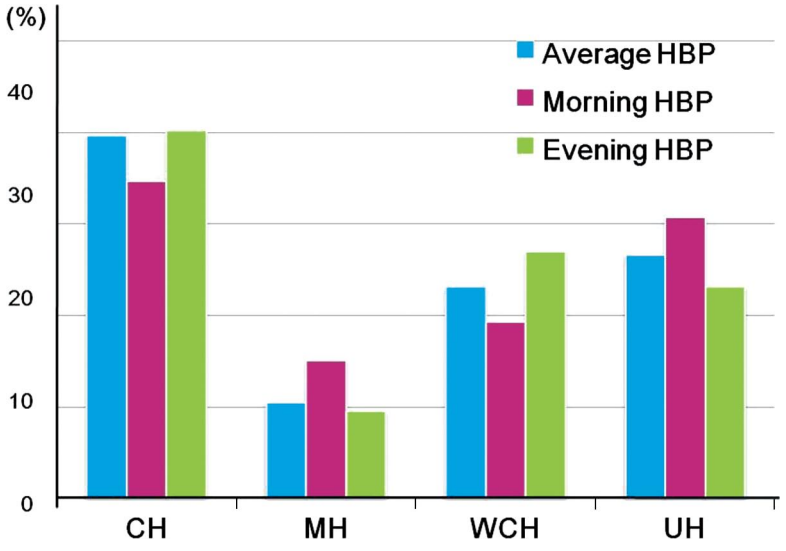

Figure 2. Comparisons of self-assessment of home blood pressure by time of measurement. Average HBP, average home blood pressure, measured average value of morning home blood pressure and evening home blood pressure; Morning HBP, morning home blood pressure, measured once every morning within 1 h of waking, before taking antihypertensive drugs; Evening HBP, evening home blood pressure, measured once every evening while seated after more than 2 min of rest 1 h before going to bed. All other abbreviations as in **Figure 1**.

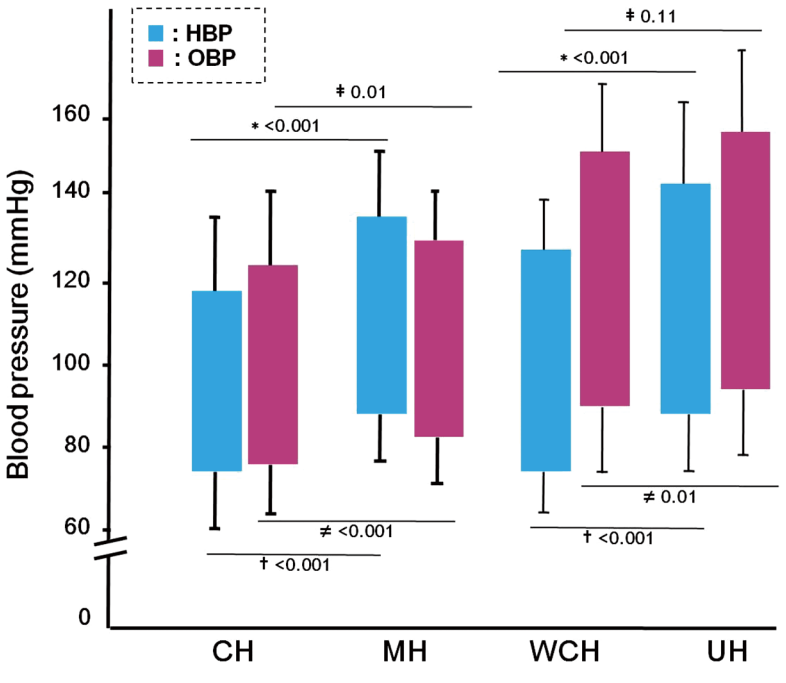

Figure 3. Office and home systolic/diastolic blood pressures in patients classified into 4 subgroup as in **Figure 1**. *P-value between CH and MH for systolic office blood pressure; †P-value between CH and MH for diastolic office blood pressure; ‡P-value between WCH and UH for systolic office blood pressure; ≠P-value between WCH and UH for diastolic home blood pressure. All other abbreviations as in **Figure 1**.

HBP minus average HBP); corrected systolic ME (coMEsbp, the value of MEsbp plus 5 mmHg). After correction, the values of coWCE and coME become closer to zero and more symmetrical to each other, because of the gap in the thresholds for normal OBP and HBP.

Laboratory Tests

Blood samples for fasting blood glucose (FBG), serum lipid profile and C-reactive protein were obtained after at least 14 h of fasting.

Statistical Analysis

All values are expressed as a mean±standard deviation. Means and proportions were compared using Student's t-test and the χ^2-test, respectively. The correlation of HBP with OBP or the ME was evaluated by bivariate correlation or multiple linear regression analysis. From the univariate comparisons, candidate predictors of MH and the ME were identified among factors that had already been identified as predictors of MH or risk factors with high probability, and were entered into logistic regression analysis models. Independent variables were selected from variables with a P value <0.3 for the 'adjustment model', and variables with a P value <0.05 were chosen for the 'reduced model'. Variables with multiple colinearity or low tolerance were excluded from the multivariate analysis model. ANOVA was used for comparisons among 3 or more groups, and the least significance difference (LSD) was used for further comparisons between groups.

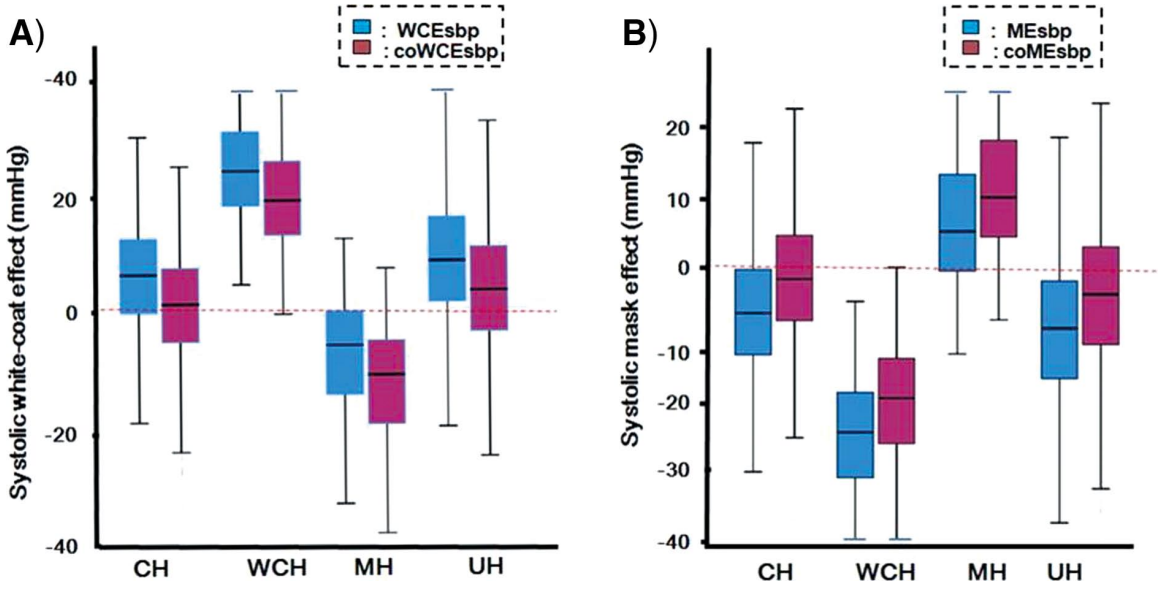

Figure 4. (**A**) White-coat effect and (**B**) ME in 4 groups of patients with hypertension. WCE, white-coat effect; coWCE, corrected white-coat effect (white-coat effect –5); ME, mask effect; come, corrected ME (ME +5). All other abbreviations as in **Figure 1**.

SPSS version 15.0 (Chicago, IL, USA) was used for the statistical calculations and P<0.05 was considered statistically significant.

Results

Study Population and Classification by BP Profile

There were 404 (39.6%) patients with CH, 107 (10.5%) with MH, 236 (23.1%) with WCH, and 272 (26.7%) with UH among the 1,019 patients. Among the 511 patients (50.1%) with COH, 107 patients (20.9%) had MH. WCH was detected in 236 patients (46.5%) in the UOH group (**Figure 1**).

We classified the patients into 4 groups according to the HBP value for the morning or evening measurement as recommended by the Japanese Society of Hypertension.[13] There were 354 (34.7%) patients with CH, 197 (19.3%) with WCH, 154 (15.1%) with MH and 314 (30.8%) with UH in the morning, and 410 (40.2%) patients with CH, 275 (27.0%) with WCH, 98 (9.6%) with MH and 236 (23.2%) with UH in the evening (**Figure 2**). Mean OBP and HBP were, respectively, 125/76 mmHg and 119/74 mmHg in the CH group, 131/80 mmHg and 138/86 mmHg in the MH group, 150/86 mmHg and 124/75 mmHg in the WCH group, and 151/90 mmHg and 142/87 mmHg in the UH group (**Figure 3**).

OBP and HBP Data

By definition, OBP was normal in clinically controlled subjects (**Figure 3**). However, OBP was slightly but significantly higher within the normal range in patients who had an abnormally elevated HBP (MH vs. CH: 130±7 vs. 125±11 mmHg for SBP and 79±7 vs. 76±8 mmHg for DBP, P<0.01 for SBP and DBP). A similar pattern was observed among clinically uncontrolled patients with abnormally high OBP, whose BP were higher in the UH than in the WCH subgroup (UH vs. WCH: 151±13 vs. 150±10 mmHg for SBP and 151±13 vs. 150±10 mmHg for DBP, P<0.01 for SBP and DBP) (**Figure 3**). OBP correlated better with the average HBP (SBP: r=0.351, P<0.001; DBP: r=0.562, P<0.001), that with either the morning measurement (SBP: r=0.299, P<0.001; DBP: r=0.417, P<0.001) or the evening measurement (SBP: r=0.355, P<0.001; DBP: r=0.438, P<0.001). Systolic OBP was also associated with systolic HBP (standardized coefficient, β=0.490, P<0.001) by multiple regression analysis, adjusted for age, BMI, FBG and total cholesterol, which were selected from the univariate comparison.

Mask Effect (Negative WCE)

WCE was investigated in each group and was highest in the WCH group (25.4±11.3 mmHg and 10.8±8.8 mmHg for systolic and diastolic WCE, respectively), followed by the UH group (9.6±14.9 mmHg and 4.9±7.8 mmHg, respectively), CH (5.9±10.1 mmHg and 2.2±7.6 mmHg, respectively) and ME (–7.5±10.6 mmHg and –6.9±7.3 mmHg, respectively) groups. The range of the WCE was wider in the WCH and UH groups than in the MH or CH group. The coWCE was close to zero (**Figure 4A**). The ME and coME had a reversed value of WCE, showing a mirror image on a graph, but the majority of patients in the MH group had positive values (**Figure 4B**). Systolic OBP correlated well with systolic HBP (r=0.351, P<0.001), whereas the systolic ME correlated better with systolic HBP (r=0.672, P<0.001) (**Figures 5A**,**B**).

Predictors of MH Among Clinically Controlled Hypertension Patients

Age and sex did not differ between the 2 groups. Patients with MH appeared to have a larger waist circumflex, a family history of premature coronary heart disease and to be accompanied more often by diabetes. Other demographic features and incidences of risk factors, such as smoking, dyslipidemia and metabolic syndrome, were similar between the 2 groups (**Table 1**).

Among the laboratory test results, the FBG level differed among the 4 groups: CH, 103.8±18.7 mg/dl; WCH, 104.7±17.8 mg/dl; MH, 111.6±35.4 mg/dl; and UH 108.9±27.3 mg/dl

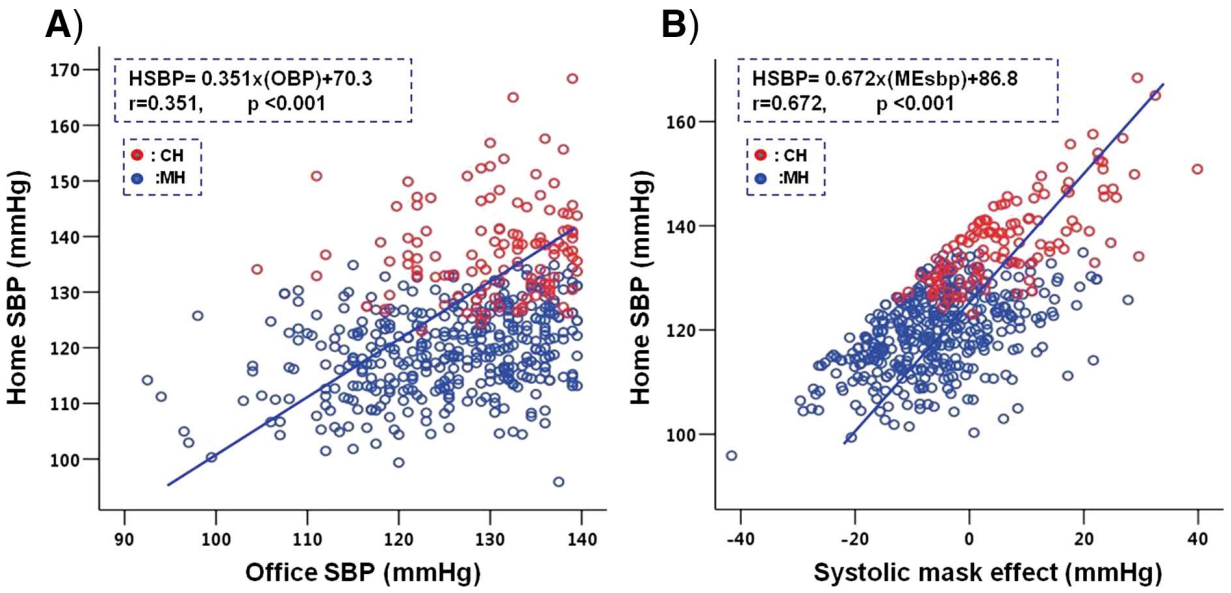

Figure 5. Correlation between office blood pressure and systolic ME in (**A**) clinically controlled and (**B**) masked hypertension. SBP, systolic blood pressure. All other abbreviations as in **Figures 1**,**4**.

Table 1. Clinical Characteristics of Clinically Controlled Hypertensive Patients in the Outpatient Clinic

	CH	MH	P value
n (%)	404 (79.1)	107 (20.9)	
Demographic features			
Sex (men, %)	174 (43.0)	54 (50.4)	0.096
Age (years)	57.2±9.3	57.0±9.0	0.822
BMI (kg/m^2)	24.8±2.8	25.7±2.9	0.068
Waist (cm)	86.8±8.0	89.6±8.5	0.024
Risk factors			
Smoking (%)	52 (13.8)	18 (16.4)	0.687
Diabetes mellitus (%)	58 (15.4)	27 (24.5)	0.028
Dyslipidemia (%)	148 (39.4)	38 (34.5)	0.242
Obesity (%)	214 (56.8)	70 (63.6)	0.610
Physical inactivity (%)	110 (29.3)	36 (32.7)	0.401
Family history (%)	31 (8.2)	3 (2.8)	0.031
Alcohol consumption (%)	127 (33.7)	43 (39.1)	0.811
Metabolic syndrome (%)	305 (80.9)	92 (83.6)	0.309
Target organ disease (%)	137 (36.3)	40 (36.4)	0.541
Laboratory data			
FBG (mg/dl)	103.8±18.7	111.6±35.4	0.025
Total cholesterol (mg/dl)	177.6±36.1	182.3±30.3	0.513
LDL-cholesterol (mg/dl)	99.7±34.2	101.3±31.1	0.979
HDL-cholesterol (mg/dl)	52.2±12.9	52.2±14.6	0.372
Triglyceride (mg/dl)	129.5±76.7	146.5±81.0	0.410
Blood pressure profile			
Systolic OBP (mmHg)	125.3±9.4	130.9±6.8	<0.001
Diastolic OBP (mmHg)	76.0±7.5	79.5±7.4	<0.001
Systolic HBP (mmHg)	119.1±7.5	138.0±8.7	<0.001
Diastolic HBP (mmHg)	73.6±6.4	86.2±6.8	<0.001
MEsbp (mmHg)	–7.11±10.32	6.16±10.13	<0.001

CH, controlled hypertension; MH, masked hypertension; BMI, body mass index; FBG, fasting blood glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OBP, office blood pressure; HBP, home blood pressure; MEsbp, systolic mask effect.

Table 2. Medications Used by Clinically Controlled Hypertensive Patients in the Outpatient Clinic

	CH	MH	P value
Antihypertensive drugs (%)			
ACEI	42 (11.1)	16 (14.5)	0.209
ARB	194 (51.5)	54 (49.1)	0.371
β-blocker	113 (30.3)	48 (43.6)	0.006
CCB	230 (61.0)	75 (68.2)	0.104
Diuretic	111 (29.4)	34 (30.9)	0.426
α-blocker	12 (3.2)	7 (6.4)	0.056
No. of antihypertensives	1.86±0.81	2.13±0.97	0.004
Other medications (%)			
Statin	135 (35.9)	34 (30.9)	0.197
Antiplatelet agent	158 (42.0)	59 (53.6)	0.015
Oral hypoglycemic	31 (8.2)	13 (11.8)	0.168

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium-channel blocker. Other abbreviations see in Table 1.

Table 3. Multivariate Analysis of Predictors of MH Among Clinically Controlled Hypertensive Patients in the Outpatient Clinic

	MH model (n=511)			
	Adjusted model		Reduced model	
	OR (95%CI)	P value	OR (95%CI)	P value
Waist (cm)	1.017 (0.988–1.047)	0.258	1.023 (0.995–1.052)	0.109
FBG (mg/dl)	1.009 (1.001–1.018)	0.020	1.010 (1.001–1.019)	0.022
Diabetes mellitus	0.965 (0.394–2.363)	0.938	0.944 (0.458–1.946)	0.876
Dyslipidemia	1.122 (0.643–1.956)	0.686	–	
Family history of premature CAD	2.540 (0.722–8.943)	0.686	2.654 (0.728–9.438)	0.746
Systolic OBP (mmHg)	1.075 (1.045–1.106)	<0.001	1.059 (1.026–1.094)	<0.001
Diastolic OBP (mmHg)	1.045 (1.007–1.084)	0.019	1.048 (0.986–1.087)	0.063
ACEI	1.009 (0.510–1.996)	0.980	–	
β-blocker	0.731 (0.441–1.211)	0.223	0.768 (0.470–1.256)	0.293
α-blocker	0.706 (0.219–2.280)	0.561	–	
Statin	1.391 (0.768–2.517)	0.276	–	
Antiplatelet agent	0.712 (0.222–2.289)	0.569	0.788 (0.324–2.398)	0.612
Oral hypoglycemic agent	0.882 (0.331–2.346)	0.801	–	
No. of antihypertensives	1.320 (1.113–1.804)	0.021	1.373 (1.062–1.776)	0.016

CAD, coronary artery disease; OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

(P=0.01 by ANOVA). Interestingly, both systolic and diastolic OBP were higher in patients with MH than in those with CH. The ME of SBP was obviously positive and higher in patients with MH than in those with CH (6.16±10.13 vs. –7.11±10.32, respectively, P<0.001). In this case, the value of the ME was the same with a negative WCE, and vice versa (Table 1). As for medications, β-blockers and antiplatelet agents, such as aspirin and clopidogrel, were used more often and the total number of antihypertensive agents commonly used by patients with MH was larger (Table 2).

Only 4 variables appeared to be associated with MH by multivariate analysis taking interactions into consideration. The probability of MH increased with the level of FBG (odds ratio (OR) 1.009; 95% confidence interval (CI) 1.001–1.018) and higher systolic OBP (OR 1.075 for each mmHg; 95%CI 1.045–1.106). MH patients took more antihypertensive medications (OR 1.320; 95%CI 1.113–1.804) (Table 3).

Patients with a positive and zero value for systolic ME ('ME ≥0': n=189, 37.2%) were compared with patients with a negative value for systolic ME ('ME <0'; n=319, 62.8%). Multivariate analysis demonstrated that FBG and systolic OBP were predictors of the ME after adjustment. To confirm the results of the adjusted model, we analyzed the data with another reduced logistic model with variables of P>0.05; FBG and systolic OBP were still predictors of a positive ME and MH, even though other variables, such as age and triglycerides, were more higher in the 'MEsbp ≥0' group (Table 4).

Patient with high FBG (>100 mg/dl) numbered 71 (61.8%) in the MH group and 192 (48.9%) in the CH group. Patients who were taking 3 or more antihypertensive medications numbered 35 (30.4%) in the MH group and 81 (20.6%) in the CH group. The value of FBG ≥100 mg/dl was chosen as the diagnostic criteria of impaired fasting glucose (IFG) according to the American Diabetic Association definition. Median values were selected for systolic and diastolic BP and the number of medications. MH was predicted with higher probability when using the following values: FBG >100 mg/dl (OR 1.692, 95%CI=1.051–2.526), systolic OBP >125 mmHg (OR 2.023 for each mmHg, 95%CI=1.200–4.412) and diastolic OBP >80 mmHg (OR 1.910 for each mmHg, 95%CI= 1.200–2.997) and >3 antihypertensive drugs (OR 1.832, 95%CI=1.120–1.140.

Table 4. Multivariate Analysis of Predictors of the Mask Eeffect Among Clinically Controlled Hypertensive Patient in the Outpatient Clinic

	MEsbp ≥0 model (n=511)			
	Adjusted model		Reduced model	
	OR (95%CI)	P value	OR (95%CI)	P value
Primary variables				
FBG (mg/dl)	0.988 (0.978–0.999)	0.027	0.987 (0.977–0.997)	0.012
Systolic OBP (mmHg)	1.111 (1.082–1.141)	<0.001	1.108 (1.080–1.137)	<0.001
Diastolic OBP (mmHg)	1.005 (0.973–1.038)	0.763	0.984 (0.951–1.018)	0.341
No. of antihypertensives	0.967 (0.739–1.265)	0.807	0.927 (0.730–1.178)	0.536
Adjustment variables				
Age (year)	0.964 (0.943–0.986)	0.002	0.964 (0.943–0.986)	0.001
Waist (cm)	0.978 (0.953–1.003)	0.089	–	
Triglycerides (mg/dl)	0.996 (0.993–0.999)	0.003	0.995 (0.993–0.998)	0.002
Smoking	0.698 (0.352–1.383)	0.303	–	
ARB	0.705 (0.472–1.055)	0.089	–	
β-blocker	1.130 (0.671–1.906)	0.645	–	
Antiplatelet agent	1.098 (0.721–1.672)	0.663	–	

Abbreviations see in Tables 1, 3.

Discussion

The major findings of this study are that MH among patients with apparently well-controlled OBP is associated with elevated FBG level, high systolic and diastolic OBP and the use of multiple antihypertensive medications. In particular, the probability of MH increased by increasing the threshold of the candidate predictors to: 100 mg/dl for FBG, 125 mmHg for systolic OBP and 3 or more antihypertensive medications. This result indicates that MH should be suspected in patients who have a high normal OBP even while taking multiple antihypertensive medications and who present with IFG.

OBP has been demonstrated to be one of the most closely associated factors with MH,[14–17] which concords with our study. In the SHEAF study involving almost 5,000 treated hypertensive patients, the probability of MH of 9% prevalence increased with systolic OBP (relative risk (RR) 1.11, 95%CI 1.14–1.99).[18] Furthermore, in a study of 1,488 hypertensive subjects, comprising MH of 10% prevalence, 2 variables (SBP <125 mmHg (RR 0.84, 95%CI 0.75–0.94) and DBP <76 mmHg (RR 0.85, 95%CI 0.76–0.96)) were found to have a negative predictive value.[19] Our result that high OBP, especially if >125/80 mmHg, has predictive value for MH suggests that such patients should have their HBP measured or undergo ABPM, even among clinically well-controlled hypertensive patients.

The FBG level was elevated more in MH patients than in those with CH, and the number of patients with IFG (defined as FBG ≥100 mg/dl by the American Diabetes Association)[20] was higher in those with MH. Patients with MH were reported to be associated with higher insulin levels than normotensive patients.[21] In our study, both the FBG level and the number of patients with IFG were higher in the MH than in the CH group. In a substudy of PAMELA, the incidence of both new-onset diabetes and IFG was much greater in patients with MH than in those with CH. The risk for patients with MH of developing diabetes or IFG is increased 2–3-fold compared with those with CH.[22] The occurrence of hypertension is also associated with abnormal glucose metabolism,[23] and insulin resistance may precede hypertension.[24] A previous study revealed that WCH or UH patients showed IFG compared with normotensive subjects.[25] In our study, MH and UH patients showed higher levels of FBG than those with CH, as in the previous study, whereas those with WCH had similar levels to those with CH. Patients with MH or UH had higher FBG levels than those with WCH, as in the previous investigation. These results suggest that IFG or insulin resistance may be associated with MH or UH, which are characterized by a higher BP that is resistant to therapy.

Taking multiple antihypertensive medications, especially 3 or more, was more common in patients with MH. In the J-HOME study, the use of at least 2 classes of antihypertensive drugs (OR 1.84, 95%CI 1.48–2.29) was associated with MH, and 48.5% of MH patients were taking 2 or more antihypertensive medications.[16] In the Ohasama study, similar results were obtained in analyses of subgroups defined on the basis of sex, use of antihypertensive medication and level of risk.[26]

The prevalence of MH in the present study was 10.5% among treated patients and 20.9% among clinically well-controlled patients by HBP measuring, which is similar to the results of other investigations.[2,20,27,28] The reported prevalence of MH varies from 7% to 23%, which includes 7–17% reported in general population-based studies[27,28] and 9–23% in studies restricted to treated hypertensive patients.[2,20] In terms of the method of out-of-clinic BP measurement, HBP self-monitoring and ABPM have detected similar percentages of MH in previous studies performed in hypertensive populations.[2,29,30] Both ABPM and HBP monitoring seem to be appropriate methods for detecting MH.

We measured HBP every day with a series of 3 consecutive measurements requested in the morning and repeated in the evening. For each patient, the average of all the available home measurements was taken as the HBP value and used for comparison with OBP levels. This method has been used in previous studies, such as PAMELA and ANBP2.[31,32] Recently, the Japanese Society of Hypertension recommended that the HBP in the morning and that in the evening should be totaled and evaluated separately, because the HBP values may have differing clinical significance because of the different measurement conditions, such as physical activity and environmental factors.[13] Hereto, we analyzed the prevalence

according to this guideline. MH was more prevalent when it was estimated from the morning-measurement data rather than from the averaged value, and was less prevalent when using the evening-measurement data (**Figure 2**). Further investigation of the worth of each totaling method is warranted with regard to the application to clinical epidemiology as well as to daily practice.

The term "reversed WCH" was coined by Wing et al,[32] but nowadays the nomenclature has been changed to MH. Similarly, the term 'negative WCE' is not appropriate because it focuses on the involvement of an alerting reaction to BP monitoring and leads clinician to think that the effect elicited by the monitoring device or attention to themselves may be greater than the one brought about by measuring BP in the clinical environment. Therefore, we recommend not using the term 'negative WCE', but to use 'ME' when evaluating the existence of MH, to ensure consistency by emphasizing that the difference between the OBP and HBP obviously depends on the HBP value.

The next issue concerning the ME is its prognostic significance. A large ME may have an adverse prognostic significance, making its identification clinically important,[33] which implies that it may be useful to more regularly obtain information not only on OBP, but also on HBP in order to correctly identify cardiovascular risk diversity and thus more correctly decide on treatment types and goals. In our study, patients with office CH and a positive ME were proved to have concordant, but not exactly the same, predictive factors as patients with MH. This result suggests that the ME may provide additive information and enhance stringency in the diagnosis of MH. However, the meaning of the ME for cardiovascular disease or long-term prognosis needs to be investigated further.

In conclusion, our data suggest that HBP monitoring might be useful for detecting MH and is highly advisable for diagnosis in well-controlled hypertensive patients who have a higher probability of MH. Given the poor prognosis linked to MH, it is important to determine the population of patients with a higher probability of MH. Three easily measured parameters could help the physician. All those individuals with a high OBP, who are taking multiple antihypertensive medication and have a high FBG level should undergo HBP monitoring, even if their BP is apparently well controlled in the outpatient clinic.

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