

Prevalence, Predictive Factor, and Clinical Significance of White-Coat Hypertension and Masked Hypertension in Korean Hypertensive patients

Eui-Seock Hwang, M.D., Kee-Joon Choi, M.D., Duk-Hyun Kang, M.D.,
Gi-Byoung Nam, M.D., Jae-Sik Jang, M.D., Young-Hoon Jeong, M.D.,
Chang-Hoon Lee, M.D., Ji-Young Lee, M.D.,
Hyun-Koo Park, M.D. and Chong-Hun Park, M.D.

*Department of Internal Medicine, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea*

Background : The prevalence and clinical significance of white-coat hypertension (WCHT) and masked hypertension (MHT) are unknown in Koreans. Here we measure the frequency of WCHT and MHT in hypertensive subjects and identify the epidemiologic and/or clinical factors that predict it in Korean subjects.

Methods : This study is a retrospective analysis of a random sample from February 2004 to October 2005. All patients had measurements of blood pressure (BP) in the clinic and 24-hour ambulatory blood pressure monitoring (ABPM). Subjects were classified into four groups on the basis of daytime ambulatory BP and clinic BP level: 1) Normotension (NT), 2) MHT, 3) WCHT, and 4) sustained hypertension (SHT).

Results : For all 967 patients, the mean clinic BP was $157.7 \pm 22.0 / 95.3 \pm 13.1$ mmHg, and the mean daytime ambulatory BP was $136.4 \pm 15.0 / 86.2 \pm 10.7$ mmHg. The NT, MHT, WCHT, and SHT groups consisted of 51 (5.3%), 55 (5.7%), 273 (28.2%), and 588 (60.8%) subjects, respectively. The left ventricular mass index was significantly higher in SHT than in the other groups, and was positively correlated with BP, especially ABPM. Compared with NT, the factors associated with MHT were younger age, male gender, higher BMI, clinic BP ≥ 130 mmHg, and alcohol consumption. Compared with SHT, the factors associated with WCHT were female gender, lower BMI, and clinic BP < 150 mmHg.

Conclusions : WCHT and MHT were prevalent in the hypertensive population. ABPM was more predictive of target organ damage than clinic BP, and could be useful in identifying subjects at risk for WCHT and MHT.

Key words : White-coat hypertension, Masked hypertension, Ambulatory BP monitoring

INTRODUCTION

Hypertension is a risk factor for diseases of the cardiovascular system. Mean daytime ambulatory blood pressure (BP) better reflects cardiovascular risk than mean clinic BP measured in a medical office, especially since daily fluctuations in BP reflect the actual BP to which individuals are exposed. Ambula-

tory blood pressure monitoring (ABPM) over 24 hours is therefore an important means of diagnosing and managing hypertension¹⁻³. With the introduction of 24-hour ABPM, conventional hypertension has been subclassified as white-coat hypertension (WCHT), in which patients exhibit elevated clinic BP but normal daytime ambulatory BP; masked hypertension (MHT), in which patients exhibit elevated daytime ambulatory BP

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• Correspondence to : Chong-Hun Park, M.D. Division of Cardiology, Department of Internal Medicine Ulsan University College of Medicine, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea Tel : 82-2-3010-3156, Fax : 82-2-486-5918
E-mail : chpark@amc.seoul.kr

but normal clinic BP; and sustained hypertension (SHT), in which patients exhibit elevated clinic and daytime ambulatory BP^{4, 5}.

WCHT is present in about 7% to 12% of the general population, and in 12% to 50% among stage 1 and 2 hypertension groups by the JNC-6 guidelines⁶⁻⁸. Factors predictive of WCHT include female gender, low educational level, low clinic BP, smoking history, and low BMI^{6, 7, 9, 10}. The degree of target organ damage¹¹⁻¹⁵ and long-term cardiovascular risk^{11, 16-18} in WCHT patients is higher than normotensive (NT) subjects, but less than in subjects with SHT.

MHT is present in about 10% of patients with hypertension^{2, 7, 8, 19}. Factors predictive of MHT include younger age, male gender, high BMI, high clinic BP, and a history of habitual drinking^{7, 20}. Target organ damage and cardiovascular risk in subjects with MHT are similar or slightly lower than those of SHT^{8, 19, 21}.

While measurement of ambulatory BP for 24 hours is essential to the diagnosis of WCHT or MHT, these conditions are not easy to diagnose in Korea, because measurements of daytime ambulatory BP are not yet common. Accordingly, we assessed the prevalence of WCHT and MHT in hypertensive patients who were followed-up with an ABPM device. We also determined the dynamic, demographic, and clinical factors predictive of WCHT and MHT, as well as their effects on target organ damage, in Korean subjects.

MATERIALS AND METHODS

Subjects

The subjects of this study were hypertensive patients ≥ 15 years old at an early stage of diagnosis who visited the outpatient unit of the Department of Cardiology at Asan Medical Center between February 2004 and October 2005, and who had undergone 24 hours of ABPM. Subjects with serious cardiovascular complications, such as coronary artery disease and stroke, at their first visit were excluded.

Methods

Demographic characteristics recorded at the first visit included age, sex, height, weight, medication, smoking history, drinking history, combined diseases, and a family history of hypertension. Blood was drawn for measurement of total serum cholesterol, triglycerides, HDL and LDL cholesterol, blood sugar, creatinine, and uric acid. Echocardiographic exams were done, depending on the doctor's decision, to obtain the left ventricular mass index (LVMI) and aortoseptal angle (AoSA). LVMI was calculated by dividing the left ventricular muscles by surface area²², and AoSA was measured from the parasternal long-axis view immediately before the opening of the aortic valve, with

AoSA increases defined as over 120° ²³.

Clinic BP and 24-hour ABPM were measured using standard procedures. If subjects were taking antihypertensive medications, they were stopped for 3 to 7 days prior to measurements of clinic BP and 24-hour ABPM. Based on mean daytime blood pressure (6 am to 10 pm) of clinic BP and 24-hour ABPM, subjects were classified into four groups^{4, 5}.

(1) Normotension (NT)

Clinic BP < 140/90 mmHg and daytime BP < 135/85 mmHg

(2) Masked hypertension (MHT)

Clinic BP < 140/90 mmHg and daytime BP ≥ 135 mmHg or 85 mmHg

(3) White-coat hypertension (WCHT)

Clinic BP ≥ 140 or 90 mmHg and daytime BP < 135/85 mmHg

(4) Sustained hypertension (SHT)

Clinic BP ≥ 140 or 90 mmHg and daytime BP ≥ 135 mmHg or 85 mmHg

Statistical Methods

Continuous variables are represented as mean standard deviation, and categorical variables as frequency and percentage. Pearson's correlation coefficient analysis was used to assess correlations between blood pressure and LVMI. The NT and MHT groups, and the SHT and WCHT were compared using chi-square tests for categorical variables and Student's t-test for continuous variables. Multivariate logistic regression analysis was used to determine whether any baseline demographic or clinical factors were predictive of MHT and WCHT. All statistical analyses were performed using SPSS 12.0 for Windows. A *p*-value < 0.05 was defined as statistically significant.

RESULTS

Baseline characteristics

The mean age of the 967 subjects was 51.9 ± 11.9 years. Of these individuals, 52% were male, 32% were current smokers, and 41.9% were habitual drinkers. In addition, 87.1% (886) were taking one or more antihypertensive medications, and 13.7% had a family history of hypertension. Overall, the mean clinic BP was $157.7 \pm 22.0/95.3 \pm 13.1$ mmHg, and the mean daytime ambulatory BP was $136.4 \pm 15.0/86.2 \pm 10.7$ mmHg. The NT, MHT, WCHT, and SHT groups consisted of 51 (5.3%), 55 (5.7%), 273 (28.2%), and 588 (60.8%) subjects, respectively (Table 1).

Compared with the NT group, the MHT group had a lower mean age, higher mean body mass index, and higher percentages of males and habitual drinkers (*p*<0.05 each). In contrast, the WCHT group had a higher percentage of females,

Table 1. Baseline characteristics of the study subjects

Variables	All subjects	Clinic BP<140/90 mmHg		<i>p</i> *	Clinic BP≥140/90 mmHg		<i>p</i> †
		NT	MHT		WCHT	SHT	
n (%)	967 (100)	51 (5.3)	55 (5.7)		273 (28.2)	588 (60.8)	
Age (year)	51.9±11.9	56.2±10.0	51.2±10.1	0.013	52.3±12.9	51.4±11.7	0.318
Sex (% woman)	48.2	60.8	93.2	0.007	62.3	41.8	<0.0001
BMI (kg/m ²)	25.2±3.1	24.3±3.0	25.8±3.3	0.021	24.8±3.3	25.4±2.9	0.005
Current smoker (%)	32.7	25.5	36.4	0.227	21.2	38.3	<0.0001
Habitual drinker (%)	41.9	23.5	47.3	0.011	32.6	47.3	<0.0001
FHx of HT (%)	13.7	7.8	5.5	0.709	13.6	15.0	0.584
Clinic BP							
Systolic	157.7±22.0	124.7±10.1	128.5±8.2	0.038	158.3±18.7	163.1±20.1	0.001
Diastolic	95.3±13.1	77.7±8.2	82.0±5.5	0.002	93.1±11.8	99.1±12.1	<0.001
Daytime BP							
Systolic	136.4±15.0	119.0±8.2	138.9±9.0	<0.0001	122.1±7.3	144.4±12.0	<0.0001
Diastolic	86.2±10.7	74.8±6.2	90.4±5.3	<0.0001	76.±5.7	91.3±9.1	<0.0001

*difference between NT and MHT

† difference between WCHT and SHT

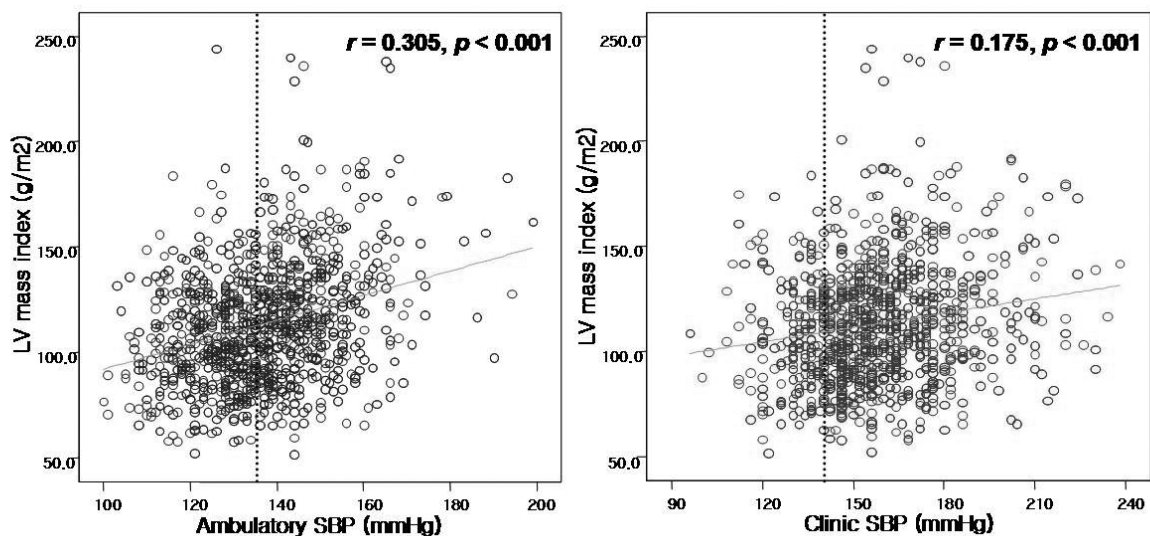


Figure 1. The association between average daytime ambulatory BP/clinic BP and left ventricular mass at echocardiography in all subjects.

a lower mean body mass index, and lower percentages of current smokers and habitual drinkers than the SHT group (*p*<0.05 each).

Echocardiographic Findings

The SHT group had a significantly higher LVMI than the WCHT group (*p*<0.05), but LVMI was not significantly different in the NT and MHT groups. LVMI showed significant positive correlations with both clinic BP (*r*=0.305, *p*<0.001) and mean daytime ambulatory BP (*r*=0.175, *p*<0.001) (Figure 1). There were no significant differences in the percentage of patients with increased AoSA.

'Masked Effect' and 'White Coat Effect'

There were significant negative correlations between clinic BP and mean daytime ambulatory BP minus clinic BP (awake ABPM-clinic BP) for both systolic (*r*=-0.8, *p*<0.001) and diastolic (*r*=-0.6, *p*<0.001) blood pressure. The white-coat effect was clear among the subjects who exhibited high clinic BP, while the masked effect was clear among subjects who exhibited low clinic BP.

Predictive Factors

We used univariate logistic regression analysis to identify predictive factors for MHT and WCHT. Factors predictive of

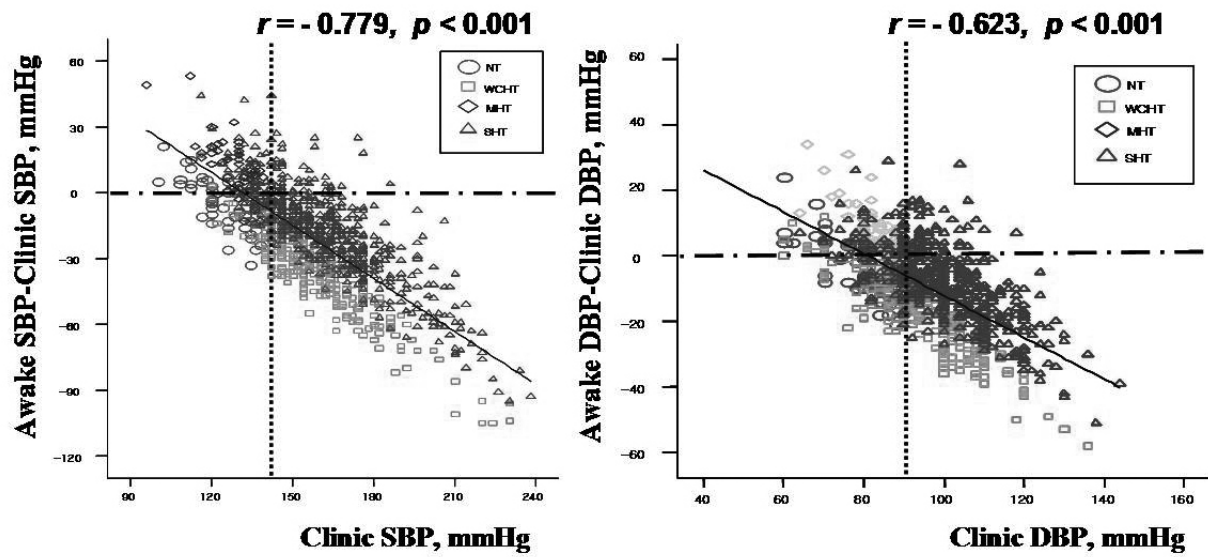


Figure 2. The ambulatory and clinic BP difference in relation to the clinic BP for all subjects. The White-coat hypertension was dominated in subjects with high clinic BP, whereas the masked hypertension was prevalent in those with lower clinic BP.

Table 2. Echocardiographic and laboratory measurements of the study subjects

Variables	All subjects	Clinic BP < 140/90 mmHg		p*	Clinic BP ≥ 140/90 mmHg		p†
		NT	MHT		WCHT	SHT	
n (%)	967 (100)	51 (5.3)	55 (5.7)		273 (28.2)	588 (60.8)	
mass index (g/m ²)	113.4±28.6	108.1±25.7	107.7±27.9	0.931	106.8±26.1	117.4±29.4	<0.0001
Increased Aorto-septal angle (%)	22.6	27.5	25.5	0.816	23.8	21.4	0.434
Total cholesterol (mg/dL)	192.9±36.0	186.9±34.9	192.3±31.6	0.417	190.4±35.9	194.6±36.4	0.119
HDL cholesterol (mg/dL)	53.0±21.9	54.2±13.1	51.1±11.8	0.215	54.8±34.3	52.3±14.9	0.264
Uric acid (mg/dL)	5.5±1.4	5.1±1.4	5.6±1.1	0.042	5.2±1.3	5.6±1.4	<0.0001

* difference between NT and MHT
 † difference between WCHT and SHT

Table 3. Predictors of Masked Hypertension

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	0.951	0.913~0.991	0.016	0.959	0.915~1.006	0.086
Sex (female vs. male)	0.314	0.154~0.751	0.008	0.333	0.128~0.866	0.024
BMI	1.168	1.019~1.339	0.026	1.204	1.034~1.401	0.017
Clinic SBP ≥ 130 mmHg	2.323	1.061~5.041	0.035	3.198	1.150~8.892	0.026
Habitual drinking (non-drink vs. drink)	0.343	0.149~0.792	0.12	0.479	0.174~1.317	0.154

MHT included younger age, male gender, higher body mass index, clinic BP ≥ 130 mmHg that did not meet hypertension criteria, and habitual drinking (Table 3). Factors predictive of WCHT included female gender, lower body mass index, and clinic BP that met the hypertension criteria but < 150 mmHg (Table 4). Multivariate logistic regression analysis showed that

factors significantly predictive of MHT were male gender, higher body mass index, and clinic BP ≥ 130 mmHg, and that factors significantly predictive of WCHT were female gender, lower body mass index, and clinic BP < 150 mmHg.

Table 4. Predictors of White-coat Hypertension

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Sex (female vs. male)	2.295	1.709~3.080	<0.001	2.092	1.529~2.864	<0.001
BMI	0.929	0.882~0.978	0.005	0.940	0.892~0.990	0.019
Clinic SBP \geq 150 mmHg	0.700	0.515~0.953	0.024	0.660	0.473~0.921	0.015

DISCUSSION

Large-scale studies in western countries on WCHT and MHT have led to JNC-7 and ESC-ESH guidelines recommending the use of ABPM for 24 hours²⁴⁻²⁶. However, ABPM is not widely used in Korea, and their prevalence is not known. Here, we assessed 24-hour ABPM in almost 1000 Korean subjects to determine the prevalence of both WCHT and MHT.

Cardiovascular risk is considerably reduced if mean daytime blood pressure, determined by ABPM, is lower than 135/85 mmHg, establishing this as the normal upper limit of ABPM^{10, 26-29}. However, many previous studies defined it as under 125/80 mmHg, leading to differences in estimates of WCHT prevalence: from around 10% in the general population and 15% to 50% among those with slightly elevated blood pressure. Its prevalence among Koreans with early stage hypertension was 28.2%, perhaps due to the fact that they were mildly hypertensive patients.

MHT, previously called 'white-coat normotension' or 'reversed WCHT', was first described as a phenomenon of normal clinic BP and high daytime ambulatory BP^{4, 30}. Its prevalence ranges from 9% to 13.4% in the general population^{8, 19} and from 7% to 22.9% in hypertensive patients^{2, 7}. The prevalence of MHT observed in this study was somewhat lower, 5.7%, probably because fewer young patients were included in the study, and therefore may not reflect primary medical practice. Furthermore, since this was not a random prospective study, we cannot exclude the possibility that MHT patients with normal clinic BP were no longer followed-up.

LVMi correlates significantly with 24-hour daytime ambulatory BP in hypertensive subjects³¹, and 24-hour daytime ambulatory BP better reflects cardiovascular risk than clinic BP^{2, 3}. We also found significant correlations between 24-hour daytime ambulatory BP and echocardiographically-determined LV hypertrophy and LVMi. In contrast to previous studies^{13, 15, 19}, however, we did not detect clear differences among the four blood pressure groups. This may have been due to the relatively low number of patients in each group, although we cannot exclude the possibility that LV hypertrophy in some patients was affected by their past medication history. It should be noted, however, that all of our subjects were recently diagnosed. Prospective studies

in large numbers of subjects are needed to determine causal relationships between BP and LV hypertrophy, as well as to determine if target organ damage affects long-term prognosis.

While the percentage of patients with AoSA increases significantly with age, there were no significant differences among the four blood pressure groups, perhaps because we did not measure the exact angle.

We also assessed factors that could distinguish between NT and MHT or between WCHT and SHT, which cannot be differentiated by clinic BP. In agreement with previous studies^{5, 7, 9, 10, 20}, we found that factors significantly predictive of MHT were younger age, male gender, higher body mass index, and clinic BP \geq 130 mmHg, while the factors significantly predictive of WCHT were female gender, lower body mass index, and hypertensive clinic BP <150 mmHg. Nicotine-induced hyperfunction of the sympathetic nerve caused by smoking contracts the peripheral vascular system and raises BP for about 30 minutes^{32, 33}. Since continual smoking raises daytime ambulatory BP and since subjects may temporarily stop smoking before visiting the clinic, measured clinic BP may be lower than daytime ambulatory BP. Thus, a previous study reported that smoking is predictive of MHT, whereas not smoking is predictive of WCHT⁹. Although we found that smoking status was not predictive of WCHT or MHT, smoking may distinguish among hypertensive groups because the percentage of smokers in the WCHT group was significantly lower than that in the SHT group.

Whereas some studies measured clinic BP two to three times per subject and averaged these values^{7, 8}, we measured clinic BP only once. Our procedure may have introduced an error in the diagnosis of WCHT by failing to reduce the white coat effect. Furthermore, the ABPM effect, in which average blood pressure increased 7/4 mmHg for the first four hours after wearing an ABPM device³⁴, could cause errors in diagnosis. Therefore, randomized, prospective studies, in which clinic BP is determined by measuring BP twice for each of three visits³⁵, and in which daytime ambulatory BP is determined by performing ABPM for 48 hours and taking the results for the second day, may more accurately determine the correlations among prevalence rates of MHT and WCHT, target organ damage, and cardiovascular risk.

In conclusion, we found that the prevalence rates of WCHT

and MHT among Korean hypertensive patients were similar to those in western countries. ABPM is essential for diagnosing such patients, and better reflects target organ damage such as LV hypertrophy. These findings indicate that ABPM should be used to determine factors predictive of WCHT and MHT, thus enabling early detection of high risk patients and providing them with proper treatment.

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