Hypertension

Clinical Predictors of Significant White-Coat Effect in Non-Diabetic Hypertensive Patients

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Background: The presence of a clinically important white-coat effect (WCE) may lead to incorrect hypertension management. The aim of our study was to investigate the possible causes of WCE in non-diabetic hypertensive patients.

Methods: Consecutive non-diabetic hypertensive patients were evaluated. A comprehensive history-taking and physical check-up were conducted. All patients received a series of studies including office blood pressure (BP), 24-hour ambulatory BP recording, and blood sampling. WCE was defined as the difference between office systolic BP (SBP) and daytime SBP. Significant WCE was defined as [(office SBP – daytime SBP)/office SBP ≥ 10%].

Results: Totally 121 patients (mean age 45.70 ± 10.61 years, 45 females) were enrolled into our study. Totally 33 patients (27.3%) had significant WCE in the study. Patients with significant WCE had more female gender ($p < 0.001$), lower body mass index ($p = 0.012$), higher office SBP ($p < 0.001$), lower office heart rate (HR, $p = 0.005$), lower triglyceride ($p = 0.008$), alanine aminotransferase ($p = 0.021$) and aspartate aminotransferase ($p = 0.008$), and higher high-density lipoprotein-cholesterol ($p = 0.039$). Multivariate analysis showed that female gender [odds ratio (OR) 3.290, 95% confident interval (CI) 1.018-10.631, $p = 0.047$], office SBP (OR 1.079, 95% CI 1.034-1.125, $p < 0.001$), and office HR (OR 0.930, 95% CI 0.885-0.978, $p = 0.005$) could predict the patients with significant WCE.

Conclusion: Significant WCE could be predicted by female gender, higher office SBP, and lower office HR. Our current study may help us to identify patients with WCE and to improve the treatment of non-diabetic hypertensive patients.

Key Words: Hypertension • Predictors • White-coat effect

INTRODUCTION

Blood pressure (BP) measurement at the clinic is currently the standard of reference. However, there is considerable debate as to the most appropriate method of assessing BP in different clinical settings. Clinic BP measurements may be inappropriate for a number of reasons, including inaccuracies in measurement technique and artificial increases in BP produced by white-coat effect (WCE).[1] Many studies have confirmed superiority of 24-hour ambulatory BP monitoring (ABPM) over office or clinic BP measurement in predicting hypertension-induced organ damage or clinical outcome.[2-5]

White-coat hypertension (WCH), defined as high BP occurring only in a medical care setting, has been reported in as many as 20% of patients in whom hypertension has been diagnosed by office BP.[6] The phenomenon that leads to it is called the WCE, which is usually defined as the difference between office BP and home or ambulatory BP. Patients with WCH appear to have more target organ damage[7,8] than normotensive subjects. WCH was also found to be a risk factor for sustained

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hypertension,[9] insulin resistance,[10] and increased all – cause mortality.[11]

Although WCE is important, it is usually ignored in clinical practice. The presence of a clinically important WCE may lead to incorrect hypertension management when decisions are based on office measurements alone. The aim of our study was to investigate the possible causes of WCE in non-diabetic hypertensives. The finding of our study will help us to identify the patients of significant WCE and to improve the treatment of these patients.

MATERIALS AND METHODS

Study patients

The data were derived from our previous data about the response to hydrochlorothiazide in non-diabetic hypertensives.[12] Patients with hypertension were prospectively included if all the following criteria were fulfilled: (1) age between 25 and 65 years; (2) sitting office systolic BP (SBP) was 140-180 mmHg and/or sitting diastolic BP (DBP) 90-110 mmHg on three different occasions within a period of 3 months, or currently on ≥ 1 antihypertensive medications without any diuretics; (3) fasting plasma sugar < 126 mg/dl; (4) there was no evidence of secondary hypertension by serial studies including blood chemistry study, renal function test, endocrine examination, abdominal sonogram, and/or renal arteriogram, etc. to exclude the possibility of chronic renal disease, renal arterial stenosis, primary aldosteronism, Cushing syndrome, pheochromocytoma, thyroid disorder, and coarctation of aorta. Patients with the following were excluded: (1) history of diabetes mellitus; (2) history of major systemic disease within recent 3 months; (3) renal dysfunction with plasma creatinin level > 1.7 mg/dL; (4) liver dysfunction with liver enzyme > 2 times the normal upper limit; (5) congestive heart failure with New York Heart Association function class II-IV; (6) pregnant women. Written informed consent was given by each patient, and the study protocol was approved by the ethics committee in Taipei VGH and Academic Sinica.

Study design

All patients were first evaluated at the clinics of the hospital. A comprehensive history-taking and physical check-up were conduct by doctors. All patients received a series of studies including office BP, body mass index, waist and hip circumference, blood sampling, 24-hour ambulatory BP recording, and electrocardiography.

Office BP was measured according to a standardized protocol by a well-trained nurse with an electronic BP monitor in the morning hours after the patients were sitting for 10 minutes in a quiet room. In each measurement, both SBP and DBP were recorded. Three consecutive BP measurements were carried out on the same upper arm each time. Each measurement was separated by a pause of 30 seconds. The average value of the last two measurements was taken as the BP record. In addition to conventional sphymomanometry, patients also underwent 24-h ABPM. The monitoring device was an Oscar oscillometric AMBP (Sun Tech Medical Instruments, Eynsham Oxfordshire, United Kingdom). The patients received the ABPM examination in the morning between 8 a.m. to 10 a.m. The device was programmed to record the BP every 15 minutes between 6 a.m. and 10 p.m. (daytime BP) and every 30 minutes from 10 p.m. to 6 a.m. (nighttime BP). Significant WCE was defined as [(office SBP – daytime SBP)/office SBP ≥ 10%].

Blood samples were obtained in the morning before eating and drug intake for analysis of blood urea nitrogen (BUN), creatinin (Cr), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), fasting blood glucose, total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-cholesterol), high-density lipoprotein-cholesterol (HDL-cholesterol), and electrolytes (Na, K, Cl). Serum concentrations of BUN, Cr, AST, ALT, TC, TG, and electrolytes were measured using a dry multilyzer analytic slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan). Serum HDL-cholesterol levels were determined with an enzymatic cholesterol assay method after dextran sulfate precipitation. The plasma glucose concentration was determined by the glucose oxidase method on a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA, USA).

Statistical analysis

All data were expressed as frequency (percentage) or mean ± standard deviation (SD). Parametric continuous data between different response groups were

compared by unpaired Student's *t*-test, and nonparametric data used the Mann-Whitney test. Categorical variables were analyzed by Chi-Square test or Fisher's Exact test. Multivariate analysis was examined by logistic regression. The results were presented as the odds ratio with corresponding 95% confidence interval. The p value was two-sided. $p < 0.05$ was considering statistically significant. Statistical analysis was performed utilizing SPSS software (Version 15.0, SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 290 consecutive patients who visited our hypertensive clinics for the evaluation of hypertension or suspected hypertension were screened. There were 121 patients (mean age 45.70 ± 10.61 years, 45 females) who received AMBP. Totally 33 patients (27.3%) had significant WCE in our study. Table 1 shows the comparison between patients with and without significant WCE. Patients with significant WCE had more female gender ($p < 0.001$), lower body mass index ($p = 0.012$), higher office SBP ($p < 0.001$), lower office heart rate ($p = 0.005$), lower TG ($p = 0.008$), ALT ($p = 0.021$), and AST ($p = 0.008$), and higher HDL ($p = 0.039$).

Table 2 shows the comparison of ambulatory BP parameters in patients with and without significant WCE. All the SBP and DBP were lower in the patients with significant WCE, including 24-hour SBP ($p < 0.001$), 24-hour DBP ($p < 0.001$), daytime SBP ($p < 0.001$), daytime DBP ($p = 0.016$), nighttime SBP ($p < 0.001$), and nighttime DBP ($p < 0.001$). All the HR were lower in the patients with significant WCE, including 24-hour HR ($p = 0.003$), daytime HR ($p = 0.001$), and nighttime HR ($p = 0.003$).

Table 1. Characteristics of subjects with and without significant white-coat effect (WCE)

	Total (n = 121)	Significant WCE (n = 33)	No significant WCE (n= 88)	p-value
Basic Characteristics				
Age (years)	45.70 ± 10.61	47.91 ± 9.84	44.91 ± 10.82	0.156
Onset of HTN (years)	39.93 ± 11.17	41.81 ± 10.86	39.26 ± 11.26	0.263
Female, n (%)	45 (37.2%)	21 (63.6%)	24 (27.3%)	< 0.001
BMI (kg/m2)	26.75 ± 4.26	25.17 ± 3.93	27.32 ± 4.24	0.012
WHR	0.87 ± 0.06	0.85 ± 0.06	0.87 ± 0.06	0.064
SBP (mmHg)	145.94 ± 15.60	157.31 ± 14.73	141.85 ± 13.84	< 0.001
DBP (mmHg)	96.57 ± 8.73	97.58 ± 10.65	96.21 ± 7.97	0.451
HR (beats/minute)	76.11 ± 13.07	70.63 ± 12.23	78.08 ± 12.86	0.005
Laboratory data				
Na (mmol/L)	142.66 ± 2.01	142.77 ± 2.84	142.62 ± 1.64	0.717
K (mmol/L)	4.30 ± 0.37	4.37 ± 0.49	4.27 ± 0.32	0.272
Cl (mmol/L)	104.17 ± 2.23	104.42 ± 2.29	104.08 ± 2.22	0.481
BUN (mg/dL)	13.03 ± 4.80	13.19 ± 5.28	12.98 ± 4.65	0.843
Cr (mg/dL)	0.89 ± 0.22	0.83 ± 0.23	0.91 ± 0.21	0.079
FBS (mg/dL)	99.50 ± 24.16	97.22 ± 15.85	100.31 ± 26.56	0.438
Cholesterol (mg/dL)	198.12 ± 39.49	195.16 ± 36.93	199.18 ± 40.52	0.609
Triglyceride (mg/dL)	159.93 ± 106.51	117.63 ± 47.88	175.13 ± 117.38	0.008
LDL-C (mg/dL)	119.95 ± 33.98	120.44 ± 31.21	119.78 ± 35.08	0.921
HDL-C (mg/dL)	45.08 ± 12.20	48.81 ± 11.45	43.74 ± 12.24	0.039
ALT (U/L)	40.88 ± 33.59	29.19 ± 21.02	45.08 ± 36.27	0.021
AST (U/L)	25.51 ± 14.37	19.78 ± 9.90	27.57 ± 15.19	0.008

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urine nitrogen; Cl, chloride; Cr, creatinine; DBP, diastolic blood pressure; FBS, fasting blood sugar; HDL-C, high-density lipoprotein-cholesterol; HR, heart rate; HTN, hypertension; K, potassium; LDL-C, low-density lipoprotein-cholesterol; Na, sodium; SBP, systolic blood pressure; WCE, white-coat effect; WHR, waist-hip ratio.

Table 2. Ambulatory blood pressure parameters of subjects with and without significant white-coat effect (WCE)

	Total (n = 121)	Significant WCE (n = 33)	No significant WCE (n = 88)	p-value
24-hour BP				
SBP (mmHg)	135.1 ± 13.9	126.6 ± 14.0	138.3 ± 12.5	< 0.001
DBP (mmHg)	88.6 ± 9.5	82.0 ± 9.2	91.1 ± 8.3	< 0.001
HR (beats/minute)	73.3 ± 11.3	69.0 ± 8.3	74.9 ± 11.8	0.003
Daytime BP				
SBP (mmHg)	138.7 ± 14.9	128.6 ± 16.0	142.4 ± 12.6	< 0.001
DBP (mmHg)	92.5 ± 10.9	87.7 ± 14.2	94.4 ± 8.7	0.016
HR (beats/minute)	77.4 ± 10.9	72.3 ± 9.7	79.3 ± 10.7	0.001
Nighttime				
SBP (mmHg)	126.1 ± 15.9	116.9 ± 16.3	129.6 ± 14.4	< 0.001
DBP (mmHg)	81.7 ± 10.3	75.7 ± 10.5	83.9 ± 9.4	< 0.001
HR (beats/minute)	65.6 ± 8.6	62.1 ± 7.2	66.9 ± 8.7	0.003

BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; WCE, white-coat effect.

Multivariate analysis showed that female gender [odds ratio (OR) 3.290, 95% confidence interval (CI) 1.018-10.631, p = 0.047], office SBP (OR 1.079, 95% CI 1.034-1.125, p < 0.001), and office HR (OR 0.930, 95% CI 0.885-0.978, p = 0.005) could predict the patients with significant WCE (Table 3).

Table 3. Determinants of significant white-coat effect

	OR	95% CI for OR	p-value
Female	3.290	(1.018-10.631)	0.047
BMI (kg/m2)	0.930	(0.808-1.071)	0.312
Office SBP (mmHg)	1.079	(1.034-1.125)	< 0.001
HR (beats/minutes)	0.930	(0.885-0.978)	0.005
Triglyceride (mg/dL)	0.995	(0.987-1.004)	0.287
HDL-C (mg/dL)	0.960	(0.913-1.010)	0.115
ALT (U/L)	1.009	(0.970-1.051)	0.651
AST (U/L)	0.963	(0.875-1.059)	0.435

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; HR, heart rate; OR, odds ratio; SBP, systolic blood pressure.

DISCUSSION

The main finding of this study showed that female gender, higher office SBP, and lower office HR could predict significant WCE. Although WCE is important, it is usually ignored in clinical practice. The finding of our study will help us to identify non-diabetic hypertensive patients with significant WCE and avoid overtreatment in these patients.

WCH is defined as high BP occurring only in a medical care setting, which is usually defined as the difference between office BP and home or ambulatory BP. WCE may be observed either in normotensive or hypertensive subjects.[13,14] In known hypertensive patients, a WCE may lead to overestimation of the severity of hypertension and to unnecessary drug prescription. Due to the possible complication of unnecessary antihypertensive medication, it is important to recognize these patients in clinic. Lindbaek et al.[15] found independent predictors of systolic WCE by including the mean ambulatory BP, age, smoking status, antihypertensive treatment and family history of cardiovascular disease. Mansoor et al.[16] reported that increasing age was associated with an increase in the level of the WCE. One study showed that negative WCE in patients with well-controlled clinic BP was associated with the presence of ischemic heart disease, and that negative WCE in the patients overall was associated with aging, male gender, and the use of antihypertensive medication.[17] In our current study, we found that female gender, high office SBP, and lower office HR predicted WCE in non-diabetic hypertensives in Taiwan. Our findings supported previous studies showing that WCE was associated with female gender and higher office BP.

The gender difference of the WCE and WCH had been noted in previous studies.[18-21] Most of these studies showed that women were more prone to have WCE than men. Myers et al.[18] found that a WCE was present in 70 of 87 women but only in 36 of 65 men ($p < 0.001$) in a total of 152 treated hypertensive patients. Female patients were more likely to have WCE than men. Martinez et al.[19] found that 136 (39%) of the 345 patients with mild to moderate hypertension were diagnosed with WCH. WCH was independently associated with female gender. Dolan et al.[20] found that the overall prevalence of WCH was 15.4% in 5,716 patients referred with elevated office blood pressure over a 22-year period. Female gender, older adults, and non-smokers were independent predictors of WCH. Ben-Dov et al.[21] found a greater magnitude of WCE in women in 3,957 patients monitored with ABPM between 1991 and 2005. In our current study, we also found that female gender was a predictor of WCE in non-diabetic hypertensives.

The mechanisms causing the WCE and WCH are unclear. Some studies suggested that it may relate to anxiety or sympathetic activity;[22-24] however, the results are conflicting.[25-27] Palatini et al.[22] reported that an exaggerated BP response to the medical environment is associated with an increased reaction to public speaking and thus reflects enhanced reactivity to the stress of daily life. Neumann et al.[23] reported that middle-aged to older men with WCH had greater sympathetic activation and diminished parasympathetic cardiac control as compared with normotensive subjects. Fagard et al.[24] also found the increased sympathetic activity and decreased parasympathetic modulation in the patients with WCH. On the contrary, Aldo Ferrara et al.[25] demonstrated that the WCE was not associated with BP reactivity to isometric exercise and cold pressure test with presumed sympathetic stimulating effects in a group of hypertensive individuals with or without metabolic syndrome. Guida et al.[26] found that the WCE was unrelated to BP responses to either isometric exercise or cold pressor test in never-treated sustained hypertensives. Tsai et al.[27] found that the WCE did not correlate to BP reactivity to mental stress in a group of never-treated mild hypertensive individuals. In our current study, WCE could be predicted by higher office SBP and lower HR. The results did not support the mechanism of sympathetic activation, which may include an increase in both BP and HR.[28] Further studies are needed to clarify the exact mechanisms.

There were some limitations in our study. First, the sample size was small. However, the BP measurement was standard, and significant predictors could be found. Second, we did not have information about smoking and concomitant medication. Further study is needed to investigate the effects of smoking and concomitant medication on WCE. Third, the clinical importance of WCE was still not known in our current study. Long-term follow-up in patients with WCE is indicated in the future.

CONCLUSION

In conclusion, significant WCE can be predicted by female gender, higher office SBP, and lower office HR. In known hypertensive patients, a WCE may lead to overestimation of the severity of hypertension and to unnecessary drug prescription. Due to the possible complication of unnecessary antihypertensive medication, it is important to recognize these patients in clinic. Our current study may help us to identify non-diabetic hypertension patients with WCE and to improve the treatment of these patients.

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