Large Discrepancy between Unobserved Automated Office Blood Pressure and Ambulatory Blood Pressure in a High Cardiovascular Risk Cohort

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Directed by Professor Sungha Park

The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science.

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ABSTRACT

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(Directed by Professor Sungha Park)

INTRODUCTION**:** Automated office blood pressure (AOBP) measurement has been shown to eliminate the white-coat effect and to be more concordant with ambulatory blood pressure monitoring (ABPM) and home blood pressure (BP) measurements. This study aimed to compare AOBP with ABPM in patients with a high cardiovascular risk.

MATERIALS AND METHODS**:** Participants were recruited from a prospective cohort study (Cardiovascular and Metabolic Disease Etiology Research Center–High Risk Cohort, clinicaltrials.gov: NCT02003781). A total of 1208 persons who had undergone both AOBP and ABPM within 7 days of each other were analyzed.

RESULTS**:** The 95% limits of agreement between systolic AOBP and daytime ABPM systolic BP (SBP) were -34.8 and 20.2 mmHg (mean difference = -7.3±14.0). The mean differences in quintiles of AOBP distributions increased with decreasing systolic AOBP (-17.8±11.2 [Q1, systolic AOBP <113 mmHg], -10.9±11.1 [Q2, systolic AOBP 113-121 mmHg], -8.5±10.7 [Q3, systolic

AOBP 121-128 mmHg], -4.2±11.8 [Q4, systolic AOBP 128-137 mmHg], 4.9±14.2 [Q5, systolic AOBP >137 mmHg], p<0.001). The prevalence of masked hypertension phenomena was 310 (25.7%) and that of white-coat hypertension phenomena was 102 (8.4%). Large discrepancies were significantly associated with lower systolic AOBP, higher atherosclerotic cardiovascular disease risk score, and history of asymptomatic cardiovascular disease.

CONCLUSION**:** The lower range of systolic AOBP exhibited a large discrepancy with daytime ABPM SBP. Moreover, higher cardiovascular risk was independently associated with larger discrepancy between AOBP and ABPM. The status of blood pressure control should be confirmed using out-of-office blood pressure measurements, even when using AOBP as a clinical BP reference in high-risk patients.

Key words: automated blood pressure measurement; blood pressure monitoring, ambulatory; hypertension; white-coat hypertension; masked hypertension

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I. INTRODUCTION

In recent years, there has been increasing interest in automated office blood pressure (AOBP), especially after the publication of the Systolic Blood Pressure Intervention Trial (SPRINT).[1] Previous studies have suggested that the mean AOBP is 15/10 mmHg lower than the mean blood pressure (BP) recorded in routine clinical practice,[2] with AOBP of 135/85 mmHg suggested as the threshold for diagnosing of hypertension.[3] Studies have also shown that AOBP measurement reduces the white-coat effect and even masked hypertension.[4-6] Accordingly, the Canadian Hypertension Education Program (CHEP) guidelines in 2016 recommended AOBP as the preferred method of in office BP measurement.[7] Moreover, the 2016 CHEP guidelines adopted the recommendation of the SPRINT, which changed the target systolic BP (SBP) for drug therapy to a systolic AOBP of <120 mmHg for patients with a high risk for cardiovascular events.[7, 8] However, in a post hoc analysis of the SPRINT ambulatory BP monitoring (ABPM) study, the clinical systolic AOBP was 6.85 mmHg lower than the daytime ABPM in the intensive treatment group

(119.67±12.84 vs. 126.52±12.32 mmHg), but 3.30 mmHg lower in the standard treatment arm (135.48±13.77 vs. 138.78±12.57 mmHg).[9] These results suggested that the AOBP and ABPM could differ from each other according to different ranges of BP, especially in persons with a high cardiovascular risk. Furthermore, most previous studies included patients with untreated hypertension or treated uncontrolled hypertension from a primary clinic.[10-12] Although these studies showed that AOBP reduces the white-coat effect and has better accuracy than manual office BP measurements, the application of their results is limited because of the relatively small study population and a lack of data on subjects with a high cardiovascular risk, who have a high prevalence of the white-coat hypertension, masked hypertension and increased BP variability.[13] Therefore, the objective of this study was to investigate the difference between AOBP and ABPM, and to assess the prevalence of masked uncontrolled hypertension and white-coat hypertension in patients with a high cardiovascular risk from a large study population.

II. MATERIALS AND METHODS

1. Study population

The study participants were recruited from a South Korean government–sponsored prospective cohort study (Cardiovascular and Metabolic Disease Etiology Research Center–High Risk Cohort [CMERC-HI]; clinicaltrials.gov: NCT02003781), which targeted patients with a high cardiovascular risk. The inclusion criteria of CMERC-HI has been published previously.[14] Briefly, the inclusion criteria were as follows: 1) high-risk hypertension defined as hypertension with at least 1 or more indication of target organ damage assessed using carotid intimal media thickness (CIMT), pulse wave velocity, ankle-brachial index (ABI), history of asymptomatic old cerebrovascular accident (CVA)/coronary artery disease, urine albumin-to-creatinine (ACR), electrocardiographic/echocardiographic left

ventricular hypertrophy, history of retinopathy on fundoscopy or chronic kidney disease (CKD, defined as estimated glomerular filtration rate [eGFR] <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$]); 2) diabetes mellitus (DM) with microalbuminuria (ACR ≥30 mg/L); 3) end-stage renal disease requiring dialysis; 4) family history of premature acute myocardial infarction (MI) (acute MI in a male first-degree relative <55 years, acute MI in a female first-degree relative <65 years); 5) asymptomatic atherosclerotic cardiovascular disease (ASCVD) (abdominal aorta diameter ≥30 mm or ABI<0.9, carotid plaque, CIMT ≥0.9 mm, asymptomatic old CVA, or >30% stenosis in at least 1 major coronary artery); 6) rheumatoid arthritis with use of methotrexate or corticosteroid; 7) atrial fibrillation with CHA2DS2-VASc score ≥1; and 8) kidney transplantation. The exclusion criteria were as follows: 1) history of acute coronary syndrome, symptomatic coronary artery disease, symptomatic peripheral artery disease, or heart failure; 2) <6 months life expectancy because of a non-cardiovascular disease (CVD); 3) pregnant or breastfeeding status; 4) history of contrast allergy and related adverse effects; or 5) kidney transplantation within the last 3 months or acute rejection after transplantation. Although atrial fibrillation was an inclusion criterion for the cohort, we excluded subjects with atrial fibrillation from the analysis.

According to these criteria, 2639 consecutive participants were enrolled in CMERC-HI from December 2013 to November 2017. We selected 1936 participants who had undergone AOBP and ABPM within 7 days of each other. Participants who had CKD stage 4,5 (eGFR <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) and kidney transplant recipients were excluded. Participants who had inadequate ABPM recordings, refused a telephone survey, lacked laboratory and demographic data, or had outlier results in systolic AOBP (<70 mmHg) were also excluded. Furthermore, as mentioned above, subjects with atrial fibrillation were excluded. Finally, 1208 participants were analyzed in this study. The disposition of the study is described in Figure 1. The study was approved by the Institutional

Review Board of the Yonsei University Health System (approval no. 4-2013-0581) and complied with the Declaration of Helsinki.

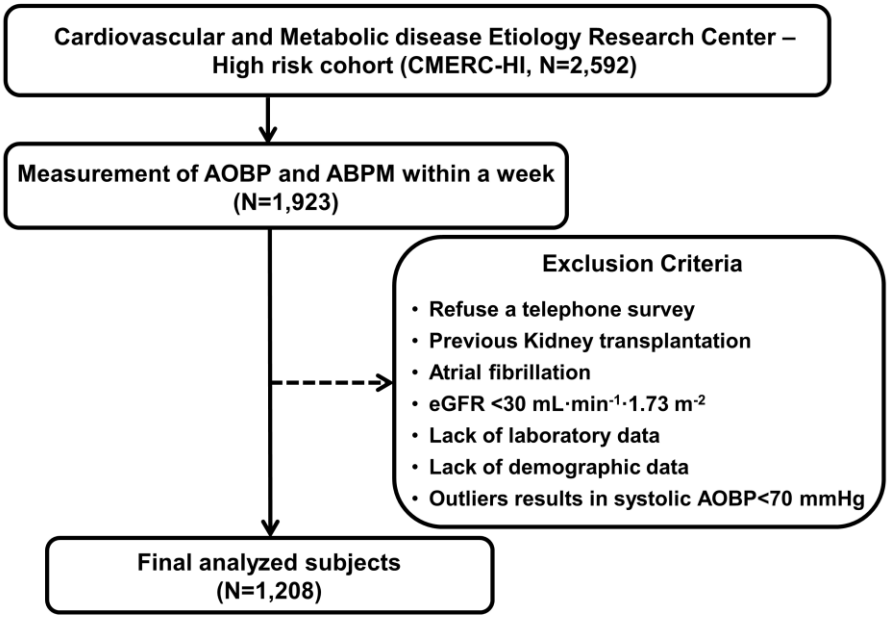

Figure 1. Disposition of the study

2. BP measurement

All participants underwent both AOBP and ABPM within 7 days from enrollment. There were no changes in medication and invasive procedures during the 7 days. AOBP measurement was performed by trained nurses in an examination room with participants in the sitting position and the right arm supported at heart level. Right mid-upper arm circumferences were measured for choosing the proper BP cuff. If the circumference was 22-32 cm, a medium-sized cuff was used. If the circumference was >32 cm, a large-sized cuff was used. AOBP was obtained using a validated automated device (HEM

7080-IC; Omron, Kyoto, Japan), which was programmed to measure sitting automatic BP at 5, 7, and 9 min.[15] After positioning the participant and setting the device, a trained nurse left the participants alone in the examination room. After 5 min of rest, automatic BP measurements at 2-min intervals were done in the examination room. After 3 measurements, a trained nurse recorded the BP data. The mean of the 3 BP readings was used as the AOBP. Twenty-four-hour ABPM readings were obtained using the Takeda TM-2430 instrument (A&D Medical, Tokyo, Japan), with readings taken every 30 min. Daytime and nighttime periods were defined according to information provided in patient diaries. Ambulatory BP readings were averaged for 24-h, daytime, and nighttime values.[14]

The white-coat effect in treated patients and white-coat hypertension in untreated patients were defined as controlled/normotensive daytime ABPM (<135/85 mmHg) but uncontrolled/elevated AOBP measurement (≥135/85 mmHg).[13, 16] We grouped patients with a white-coat effect and those with white-coat hypertension together as patients with the white-coat hypertension phenomena. Masked uncontrolled hypertension was defined as controlled AOBP measurement (<135/85 mmHg) but uncontrolled daytime ABPM (≥135/85 mmHg) in treated patients.[13] Untreated patients in the same situation were designated as having masked hypertension. We defined patients with masked uncontrolled hypertension or masked hypertension as having the masked hypertension phenomena.

3. Statistical analysis

All continuous data are presented as mean ± standard deviation, and categorical data are reported as numbers and percentages in each group. eGFR was calculated from serum creatinine by using the CKD Epidemiology Collaboration equation.[17] To estimate the cardiovascular risk of cohort participants, the Framingham 10-year CVD risk score and 10-year risk of

developing a first ASCVD were calculated.[18, 19] Agreement between AOBP and daytime ABPM was assessed using a Bland-Altman plot.[20] Comparison of the mean differences between systolic AOBP and daytime ABPM SBP according to quintiles of the systolic AOBP distribution was performed using a one-way analysis of variance with Turkey's test. To investigate the independent determinants of the difference between systolic AOBP and daytime ABPM SBP, multiple regression analysis was performed. Multivariate logistic regression analysis was performed to determine the predictors of a discrepancy of SBP ≥20 mmHg between systolic AOBP and daytime ABPM SBP. All tests were 2-sided, and statistical significance was defined as $p<0.05$. All statistical analyses were performed with R statistical software (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

III. RESULTS

1. Baseline characteristics

The baseline characteristics and BP measurements of the 1208 participants are shown in Table 1. Briefly, the average age of the study population was 61.4±11.0 years, and 629 (52.1%) were men. Most of the participants had been treated with antihypertensive medication (n=1040, 86.1%), and 532 (44.0%) had DM. The mean eGFR was 82.6±20.9 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and 203 (16.8%) of participants had 30-60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ of eGFR. The mean 10-year Framingham CVD risk score was 19.4±14.5%, and 623 (51.6%) of the participants had >15% of the Framingham CVD risk score. The mean 10-year risk of developing a first ASCVD was 15.3±13.4%, and 776 (64.2%) of the participants had a score >7.5% of the risk score. The mean systolic/diastolic AOBP was 125.9±14.7/74.7±9.5 mmHg, which was 7.3/5.2 mmHg lower than the daytime ABPM. The mean nighttime ABPM SBP/diastolic BP (DBP) was 118.5±15.3/70.5±8.2 mmHg, and the mean 24-h ABPM SBP/DBP was 127.9±12.9/76.5±7.3 mmHg.

Table 1. Baseline characteristics of the study population

Characteristics	Values
Number of patients, n	1,208
Age, years ± SD	61.4 ± 11.0
Male gender, n (%)	629 (52.1%)
BMI, kg/m^2 ± SD	25.5 ± 3.5
Current smoker, n (%)	160 (13.3%)
Family history of CVD, n (%)	318 (26.3%)
*History of asymptomatic CVD, n (%)	253 (20.9%)
Diabetic mellitus, n (%)	532 (44.0%)
Hyperlipidemia, n (%)	756 (62.6%)
Treated hypertension, n (%)	1040 (86.1%)
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$± SD	82.6 ± 20.9
†Chronic kidney disease, n (%)	203 (16.8%)
Framingham 10-yr CVD risk score, % ± SD	19.4 ± 14.5
10-year risk of ASCVD, mean, % ± SD	15.3 ± 13.4
Angiotensin receptor inhibitor, n (%)	815 (67.5%)
ACE inhibitor, n (%)	67 (5.5%)
Beta blocker, n (%)	311 (25.7%)
Calcium channel blocker, n (%)	627 (51.9%)
Diuretics, n (%)	336 (27.8%)

Aspirin, n (%)	349 (28.9%)
Statin, n (%)	769 (63.7%)

	Systolic	**Diastolic**
AOBP, mmHg ± SD	125.9 ± 14.7	74.7 ± 9.5
Daytime ABPM, mmHg ± SD	133.2 ± 13.4	79.9 ± 7.9
Nighttime ABPM. mmHg ± SD	118.5 ± 15.3	70.5 ± 8.2
24hour ABPM, mmHg ± SD	127.9 ± 12.9	76.5 ± 7.3

Data are expressed as the number (%) or mean ± SD.

*Asymptomatic old cerebrovascular accident and coronary artery stenosis

†Participants with eGFR 30-60 mL·min^{-1}·1.73 m^{-2} (eGFR <30 were excluded)

BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; AOBP, automated office blood pressure; ABPM, ambulatory blood pressure monitoring

2. Agreement of AOBP with ABPM

In the Bland-Altman analysis, the limits of agreement were -34.8 and 20.2 mmHg (Figure 2A), and the mean difference between systolic AOBP and daytime ABPM SBP was -7.3 mmHg (95% confidence interval [CI]: -8.1 to -6.5). The limits of agreement between diastolic AOBP and daytime DBP were -22.3 and 12.0 mmHg, and the mean difference was -5.2 mmHg (95% CI: -5.7 to -4.7) (Figure 2B).

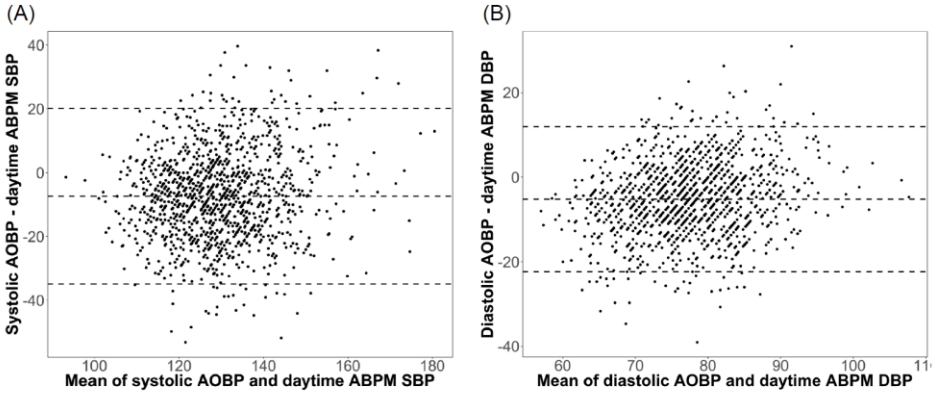

Figure 2. Bland-Altman plot comparing the difference (A) between systolic AOBP and daytime ABPM SBP, and (B) between diastolic AOBP and daytime ABPM DBP

The mean difference between AOBP and daytime ABPM in participants with systolic AOBP ≥135 mmHg (n=291) was 3.7±14.2/-1.2±9.3 mmHg, and that in participants with systolic AOBP <135 mmHg (n=917) was -10.8±12.1/-6.5±8.2 mmHg. Among 1040 of the treated patients, 785 had systolic AOBP <135 mmHg and 240 had systolic AOBP >135 mmHg (Table 2). A total of 168 participants had not been treated for hypertension. Among them, 132 had systolic AOBP of <135 mmHg and 36 had systolic AOBP of ≥135 mmHg. The mean differences between systolic AOBP and daytime ABPM SBP in participants with systolic AOBP ≥135 mmHg were 3.7±14.1/-1.4±9.3 mmHg in treated patients and 3.7±14.7/-0.2±9.3 mmHg in untreated patients. The mean difference between systolic AOBP and daytime ABPM SBP in participants with systolic AOBP <135 mmHg was -10.5±12.3/-6.5±8.2 mmHg in treated patients and -12.2±10.6/-6.1±8.1 mmHg in untreated patients, as shown in Table 2. Among patients who experienced the white-coat hypertension phenomena, 92 were treated and 10 were untreated. A total of 17 treated patients and 2 untreated patients with systolic AOBP <135 mmHg had the white-coat

hypertension phenomena because their diastolic AOBP was >85 mmHg but their daytime ABPM DBP was <85 mmHg.

Table 2. Comparison between AOBP and ABPM according to treatment status and AOBP ≥135 mmHg or <135 mmHg

	Total patients	Treated patients		Untreated patients	
	Total (n=1208)	Systolic AOBP <135mm Hg (n=785)	Systolic AOBP ≥135mm Hg (n=255)	Systolic AOBP <135mm Hg (n=132)	Systolic AOBP ≥135mm Hg (n=36)
Mean systolic AOBP, mmHg ± SD	125.9 ± 14.7	119.8 ± 9.2	145.6 ± 9.4	117.8 ± 9.8	147.5 ± 12.9
Mean diastolic AOBP	74.7 ± 9.5	72.5 ± 8.4	80.9 ± 9.4	73.2± 8.6	86.0 ± 9.5
Mean daytime ABPM SBP	133.2 ± 13.4	130.4 ± 12.0	142.0 ± 14.1	130.3 ± 10.6	143.8 ± 13.5
Mean daytime ABPM DBP	79.9 ± 7.9	79.0 ± 7.6	82.3 ± 8.3	79.2 ± 7.3	85.8 ± 7.6
Mean SBP difference	-7.3 ± 14.0	-10.5 ± 12.3	3.7 ± 14.1	-12.2 ± 10.6	3.7 ± 14.7
Mean DBP difference	-5.2 ± 8.7	-6.5 ± 8.2	-1.4 ± 9.3	-6.1 ± 8.1	-0.2 ± 9.3
*White-coat hypertension	102 (8.4%)	‡17 (2.2%)	75 (29.4%)	‡ 2 (1.5%)	8 (22.2%)
†Masked hypertension	310 (25.7%)	262 (33.4%)	0 (0.0%)	48 (36.4%)	0 (0.0%)

Data are expressed as the number (%) or mean ± SD.

*White-coat effect, masked uncontrolled hypertension: treated hypertensives,

†White-coat hypertension, masked hypertension: untreated subjects.

‡ The number of patients with white-coat hypertension phenomena because their diastolic AOBP was ≥85 mmHg, but daytime ABPM DBP was <85 mmHg. AOBP, automated office blood pressure; ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure

The number of participants with the white-coat hypertension phenomena was 102 (8.4%) among the total population. The number of patients who had masked uncontrolled hypertension was 262 and that of patients with masked hypertension was 48. The total number of participants with the masked hypertension phenomena was 310 (25.7%).

The ranges of systolic AOBP in quintile distributions of systolic AOBP were <113 mmHg (Q1, n=242), 113-121 mmHg (Q2, n=242), 121-128 mmHg (Q3, n=241), 128-137 mmHg (Q4, n=242), and >137 mmHg (Q5, n=241), as shown in Table3. The mean differences between systolic AOBP and daytime ABPM SBP increased significantly from Q5 (4.9±14.2 mmHg) to Q1 (-17.8±11.2 mmHg).

Table 3. Comparison between AOBP and ABPM in quintile distributions of systolic AOBP

	Q1 (n=242)	Q2 (n=242)	Q3 (n=241)	Q4 (n=242)	Q5 (n=241)
Ranges of systolic AOBP, mmHg	<113	113-121	121-128	128-137	>137

Mean systolic AOBP *	107.2±5	117.4±2	124.8±2	132.1±3	147.9±10
Mean diastolic AOBP *	66.4±7	72.2±7	74.7±8	78.7±8	81.8±10
Mean daytime ABPM SBP *	125.0±11	128.4±11	133.3±11	136.3±12	143.0±14
Mean daytime ABPM DBP *	76.7±7	78.4±8	80.2±7	81.5±8	82.8±9
Mean difference, SBP*	-17.8±11	-10.9±11	-8.5±11	-4.2±12	4.9±14
Mean difference, DBP*	-10.3±8	-6.2±7	-5.5±8	-2.9±8	-1.0±9
White-coat hypertension phenomena, n	0 (0%)	3 (1.2%)	6 (2.5%)	27 (11.2%)	66 (27%)
Masked hypertension phenomena	49 (20%)	74 (30.6%)	104 (43.2%)	83 (34.3%)	0 (0%)

Data are expressed as the number (%) or mean ± SD.

*P<0.05 from all other quintile

AOBP, automated office blood pressure; ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure

Figure 3 presents the gradual changes in mean differences per 5 mmHg increase in systolic AOBP. The mean difference was minimized when systolic AOBP was 131-135 mmHg (-2.7±11.2, n=122), gradually increased with a decrease in systolic AOBP, and was maximized when systolic AOBP was <110 mmHg (-19.1±11.3 mmHg, n=142).

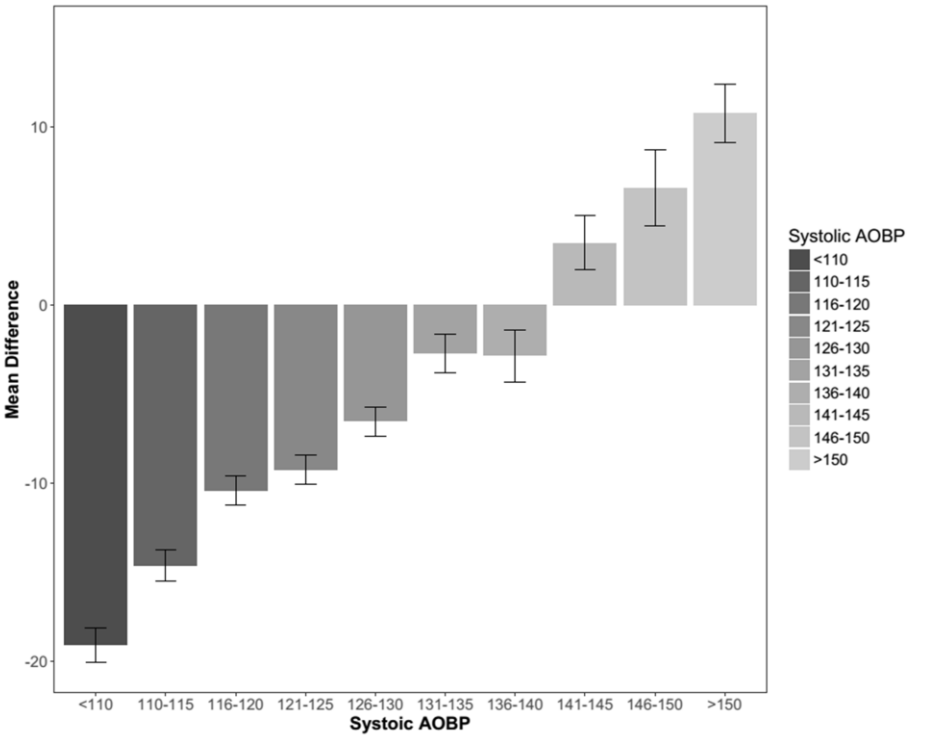

Figure 3. Changes in mean differences per 5 mmHg increase in systolic automated office blood pressure (AOBP).

3. Determinants of discrepancy

Table 4 presents the significant determinants for a higher discrepancy between systolic AOBP and daytime ABPM SBP. The results showed that increased systolic AOBP was associated with a lower discrepancy between systolic AOBP and daytime ABPM SBP. Furthermore, a higher ASCVD risk score and a history of asymptomatic CVD were independently associated with an increased discrepancy between systolic AOBP and daytime ABPM SBP. The independent determinants for a discrepancy between systolic AOBP and daytime ABPM SBP of ≥20 mmHg are shown in the right side of Table 4. The analysis showed that every 10 mmHg increase in systolic AOBP was significantly associated with a lower discrepancy between systolic AOBP and daytime ABPM SBP. On the

other hand, a higher ASCVD risk score and a history of asymptomatic CVD were significantly related to a large discrepancy between systolic AOBP and daytime ABPM SBP of ≥20 mmHg.

Table 4. Determinants of the difference between systolic AOBP and daytime ABPM SBP, and discrepancy between systolic AOBP and daytime ABPM SBP of ≥20 mmHg

Variables	*Absolute value of difference (R^2=0.052)			†Discrepancy of SBP >20 mmHg (n=254)	
	β ± Standard error	t value	P value	Odds ratio (95% CI)	P value
Systolic AOBP (+10mmHg)	-0.209 ± 0.193	-6.893	<.001	0.72 (0.64-0.80)	<.001
ASCVD risk score (+1%)	0.104 ± 0.023	3.192	0.002	1.02 (1.01-1.04)	<.001
Body mass index	0.032 ± 0.076	1.136	0.183	1.01 (0.98-1.06)	0.392
‡History of asymptomatic CVD	0.115 ± 0.649	4.093	<.001	1.51 (1.08-2.09)	0.013
Familiar history of CVD	0.009 ± 0.611	0.329	0.675	1.13 (0.81-1.56)	0.471
eGFR	0.029 ± 0.014	0.943	0.348	1.00 (0.99-1.01)	0.254
Binge drinking	-0.002 ± 1.015	-0.079	0.937	1.03 (0.59-1.74)	0.907

*Absolute value of difference between systolic AOBP and daytime ABPM SBP
†Difference between systolic AOBP and daytime ABPM SBP more than ±20mmHg, ‡Asymptomatic old cerebrovascular accident/ coronary artery stenosis; SBP, systolic blood pressure; AOBP, CI, confidence interval; automated office blood pressure; CVD, cardiovascular disease; eGFR,

estimated glomerular filtration rate

IV. DISCUSSION

The main findings of this study were as follows: 1) the lower range of systolic AOBP was associated with a larger discrepancy with daytime ABPM SBP. 2) a higher cardiovascular risk was associated with a larger discrepancy between systolic AOBP and daytime ABPM SBP. 3) there was a high prevalence of the masked hypertension phenomena when using AOBP as the clinical BP reference in this high cardiovascular risk cohort. 4) the prevalence of white-coat hypertension phenomena, as expected, was lower than that reported in studies using conventional office BP measurements.

A key finding of this study was the relatively large mean difference and poor limits of agreement compared with those in previous reports. Myers et al. reported a mean estimated difference between awake ambulatory BP and AOBP of -1.8/-2.9 mmHg at post-enrollment and -2.8/-4.6 mmHg at 2 years follow-up.[10] Godwin et al. also demonstrated a mean difference of AOBP with awake ambulatory BP of 1.8/-0.2 mmHg.[11] In other studies with samples sizes ≥300, the mean SBP difference was -5.0 to 1.1 mmHg.[6, 11, 12, 21, 22] The inconsistent findings may be due to population differences and different ranges of BP. Almost all of the previous studies included patients with clinical BP >140/90 mmHg[4, 11] or patients who were referred by primary physicians for ABPM.[6, 21] Therefore, most of the study population comprised patients who were suspected of having uncontrolled hypertension, with their mean systolic AOBP being between 131 and 140.5 mmHg. In contrast, we did not exclude participants with normal BP; thus, we included those who were predominantly being treated for hypertension and had a relatively wide range of BP measurements. Consequently, the mean systolic AOBP in this study was 125.9±14.7 mmHg, and 60% (Q1-Q3) of the participants had systolic AOBP <128 mmHg. In our study, the mean SBP/DBP differences (3.7/-1.4 mmHg)

obtained in patients with systolic AOBP ≥135 mmHg were comparable to those of previous reports.

The mean estimated difference was minimized at a systolic AOBP of 128-137 mmHg, but progressively increased with decreasing range of systolic AOBP, with the mean difference in those with a systolic AOBP <113 mmHg being -17.8 mmHg. These results are supported by the study of Godwin et al., which indicated that AOBP is less accurate when labeling subjects as having normal SBP (<130 mmHg).[11] In a meta-analysis by Jegatheswaran and et al., who analyzed 19 studies with a median sample size of 226, the weighted mean difference between the 2 methods for SBP was only -1.52 mmHg. However, the study level difference in mean SBP was -9.7 to 9 mmHg with large heterogeneity, suggesting that the discrepancy between the two methods may vary widely according to the study population.[23] In our study, the large difference between AOBP and ABPM with decreasing AOBP values resulted in a high prevalence of the masked hypertension phenomena. In a Spanish registry data of 12897 treated hypertensive subjects, the proportion of masked uncontrolled hypertension was 5.4%.[24] Although the demographic characteristics of our cohort, with a high prevalence of subjects with a high cardiovascular risk and diabetes, predisposes them to a higher risk of masked hypertension, the discrepancy is large enough to suggest that unattended AOBP measurement increases the chance for the masked hypertension phenomena. These results are supported by a study of Edward et al, who reported that AOBP increases the prevalence of masked effect (20%), compared with manual office BP (8%)[12]. In the latest Hypertension Canada guidelines, a target SBP of ≤120 mmHg measured using AOBP is recommended for high-risk patients aged ≥50 years.[25] Considering that our study cohort consisted of high-risk subjects (average age, 61.4 years) with large differences between AOBP and daytime ABPM, and with a high prevalence of masked hypertension in those with systolic AOBP ≤121 mmHg, we believe that this study has important clinical

implications in that, even in those with well-controlled clinical BP as assessed using unattended AOBP measurements, assessment of out-of-office BP measurements with ABPM is necessary to confirm the status of BP control. This is especially important considering that intensive BP lowering is recommended in high-risk subjects who are also at an increased risk for masked hypertension.

Another key finding of this study was that a higher ASCVD risk score and a history of asymptomatic cardiovascular disease were independent determinants of a larger discrepancy between systolic AOBP and daytime ABPM SBP. As most of the studies validating the clinical accuracy of AOBP were done on patients who were referred from primary clinics, they were more likely than not to have a lower risk of CVD. This may be one explanation for the difference between the results of our study from those of previous studies. This finding is supported by the results of the SPIRNT ABPM study, which demonstrated that the mean difference in the intensive treatment group (systolic AOBP=119.67±12.84 mmHg, mean difference= -6.85 mmHg) was higher than that in the standard treatment group (systolic AOBP=135.48±13.77 mmHg, mean difference= -3.30 mmHg) among patients with a high cardiovascular risk (mean 10-year Framingham CVD risk score=20.8 %).[9] Subjects with a high cardiovascular risk are known to be at an increased risk for masked hypertension and increased BP variability.[13] Moreover, old age and CKD, which were relatively more prevalent in our cohort, have been shown to be independent risk factors for increased BP variability.[26, 27] Therefore, in subjects with a high cardiovascular risk and those with a higher risk of increased BP variability, physicians should be aware of a larger discrepancy between AOBP and ABPM, especially in subjects who are considered to have well-controlled hypertension according to the AOBP measurement.

The white-coat hypertension phenomena, including white-coat hypertension and white-coat effect, is known to be diminished with unobserved AOBP. Myers et al. reported that the proportion of white-coat effects, defined as an office BP

higher than the mean awake ABPM by at least 20 mmHg systolic and/or 10 mmHg diastolic in treated patients, was lower when using AOBP than with manual office BP (12% vs. 65%, $p<0.001$).[6] As we did not measure conventional office BP in this study, the prevalence of the white-coat hypertension phenomena based on AOBP could not be directly compared with the prevalence based on the manual office BP measurement. However, the prevalence of the white-coat hypertension phenomena (8.4%) was relatively lower than in previous reports. In the registry data for 12897 treated hypertensives, the prevalence of white coat hypertensives was 33.4%.[24] Thus, subjects with uncontrolled SBP as assessed using AOBP are much less likely to show white-coat hypertension than those assessed using conventional BP measurement. However, in a study by Godwin et al., 134 patients (30.7%) had an awake ABPM SBP of <135 mmHg out of 436 patients with AOBP ≥135/85 mmHg.[11] Similar results were observed in our study in 83 (28.5%) of 291 patients with systolic AOBP ≥135 mmHg, who were confirmed to have the white-coat hypertension phenomena. Moreover, the difference between systolic AOBP and daytime ABPM SBP in subjects with AOBP >137 mmHg was 4.9 mmHg, which is close to the standard reference for the difference between clinical SBP and daytime ABPM SBP of 5 mmHg.

This study has several limitations. First, AOBP was measured using HEM 7080-IC, a fully automated oscillometric device that has been validated for home BP monitoring. Although the device has not been validated as an office BP measurement device, we assumed that as a fully automated device that has been validated for its accuracy, it can be used as an accurate tool for unattended AOBP measurement. Second, AOBP in this study was obtained as a mean of 3 BP measurements, whereas many of the previous studies used an average of 5 BP measurements. We postulated that 3 BP measurements may be sufficient to achieve a generally recommended method of AOBP measurement, as a recent study reported that only 2 AOBP readings taken over 6 min were enough to be

comparable with daytime ABPM.[28] Third, this study was a cross sectional analysis of AOBP measured in a single sitting compared with ABPM. Therefore, we cannot rule out the possibility that the prevalence of masked hypertension would have decreased with subsequent measurements of AOBP. In the CAMBO masked hypertension sub-study, the number of patients with masked hypertension has been shown to decrease with multiple visits in the office.[5]

V. CONCLUSION

In this cohort of subjects with a high cardiovascular risk, the lower range of systolic AOBP exhibited a large discrepancy with daytime ABPM SBP and a high prevalence of masked hypertension. Also, higher cardiovascular risk was independently associated with increase in discrepancy between AOBP and daytime ABPM. When considering intensive BP control of high risk subjects, the status of BP control should be confirmed using out-of-office BP measurement, even when using AOBP as a clinical BP reference.

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ABSTRACT(IN KOREAN)

비관찰 자동혈압측정검사와 24시간 혈압측정검사 사이의 높은 수준의 불일치: 심혈관질환 고위험군 코호트 연구

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서론: 비관찰 자동혈압의 측정은 백의고혈압의 빈도를 줄이고 24시간 혈압측정검사와 높은 수준의 일치도를 보이는 것으로 알려져 왔다. 본 연구는 심혈관 질환 고위험 환자를 대상으로 자동혈압 측정과 24시간 혈압측정검사를 비교를 목적으로 한다.

재료 및 방법: 심뇌혈관 고위험군 맞춤예방 연구 (Cardiovascular and Metabolic Disease Etiology Research Center–High Risk Cohort, clinicaltrials.gov: NCT02003781) 환자 중 비관찰 자동혈압 측정과 24시간 혈압측정검사 모두를 7일 이내에 시행한 1208명의 환자를 대상하여 분석하였다.

결과: 수축기 자동혈압 측정결과와 낮시간 수축기 혈압의 평균 차이에 대한 95% 신뢰구간은 -34.8 과 20.2 mmHg (평균 차이=-7.3±14.0) 였다. 대상 환자를 수축기 자동혈압에 따라 5분위로 분류 하였을 때 평균 혈압의 차이는 수축기 자동혈압이

감소함에 따라 증가하였다. (-17.8±11.2 [Q1, 수축기 자동혈압 <113 mmHg], -10.9±11.1 [Q2, 수축기 자동혈압=113-121 mmHg], -8.5±10.7 [Q3, 수축기 자동혈압=121-128 mmHg], -4.2±11.8 [Q4, 수축기 자동혈압= 128-137 mmHg], 4.9±14.2 [Q5, 수축기 자동혈압 >137 mmHg], p<0.001).

가면 고혈압의 발생은 310 (25.7%)였고 백의 고혈압의 발생은 102 (8.4%)로 나타났다. 양 혈압 측정 결과의 차이의 정도는 낮은 자동혈압측정 결과, 높은 심혈관 질환의 위험도, 무증상 심혈관 질환의 유무와 독립적으로 유의미하게 관련이 있었다.

결론: 수축기 자동혈압측정상 낮은 혈압이 측정된 환자에서 자동화혈압측정과 24시간 혈압측정사이의 일치도가 더 낮은 것으로 확인되었다. 또한 심혈관질환의 위험도는 이러한 낮은 일치도와 독립적 연관이 있었다. 따라서 심혈관질환 고위험군 환자에서 혈압 조절 정도의 여부는 반드시 진료실 밖 혈압 측정으로 확인하여야 한다.

핵심되는 말 : 자동혈압측정검사, 24시간 혈압측정검사, 고혈압, 백의 고혈압, 혈압측정