



Comparison of blood pressure values—self-measured at home, measured at an unattended office, and measured at a conventional attended office

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Received: 15 March 2019 / Revised: 21 May 2019 / Accepted: 25 May 2019 / Published online: 21 June 2019
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Abstract

Self-measured blood pressure (BP) at home (HBP) has been commonly used in clinical practice. Although the unattended office BP (UBP), in which a patient is left alone before and during the measurement, has been investigated, the advantages of UBP over HBP or conventionally measured attended office BP obtained using automated devices (CBP) remain unclear. We performed a multicenter clinical study in Japan to compare the UBP, CBP, and HBP among 308 patients with hypertension at 3 clinics (women, 57.8%; mean age 71.8 years; under antihypertensive drug therapy, 96.4%). The patients measured HBP twice in the morning and twice in the evening for 5 days according to the Japanese Society of Hypertension guidelines. Using the Omron HEM-907 cuff-oscillometric device, the UBP and CBP were measured in line with the protocol in the Systolic blood PResure INtervention Trial (SPRINT) and in accordance with the guidelines, respectively. Correlation coefficients were ≤ 0.16 for the comparison of UBP versus morning and evening HBP for the systolic measurement, whereas they were approximately 0.5 ($P < 0.001$) for the diastolic measurement. The difference between UBP minus HBP was small on average but varied among individuals (mean \pm SD for UBP minus morning HBP: $0.9 \pm 17.8/-4.5 \pm 10.5$ mmHg; UBP minus evening HBP: $5.7 \pm 17.8/-0.1 \pm 11.3$ mmHg). In contrast, the measurement values of CBP and UBP were highly correlated ($r \geq 0.72$), but the difference between CBP minus UBP was $10.4 \pm 12.0/4.2 \pm 6.5$ mmHg. Based on the low correlations and wide range of differences, UBP cannot be used as an alternative to HBP.

Keywords Conventional office blood pressure. Automated office blood pressure. Home blood pressure. Patient population. Attended and unattended measurement

Introduction

Self-measured blood pressure (BP) at home (HBP) has been commonly used in clinical practice. HBP can identify white-coat and masked hypertension [1, 2], and has a stronger prognostic ability for cardiovascular complications

than conventional office BP measured by medical staff [3–5]. Because ambulatory BP monitoring has been limited in its dissemination by practical and economic concerns [6], HBP measurement may become a practical and reliable standard for out-of-office BP measurement. The Japanese Society of Hypertension Guidelines for the Management of Hypertension published in 2014 (JSH 2014) [7] led the world in promoting the prioritization of HBP measurement for the diagnosis and treatment of hypertension in routine clinical practice.

Advantages of so-called automated office BP (AOBP) measurement have been highlighted [8, 9] following the publication of impressive results in the Systolic blood PResure INtervention Trial (SPRINT), wherein significant

Supplementary information The online version of this article (<https://doi.org/10.1038/s41440-019-0287-6>) contains supplementary material, which is available to authorized users.

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reductions in cardiovascular complications (by 25%) and even mortality (by 27%) were demonstrated among patients whose AOBP was treated to achieve a target of <120 mmHg for systolic BP compared with a target of <140 mmHg [10–12]. However, the characteristics of AOBP have yet to be well defined. The initial definition of AOBP [13, 14] does not include antecedent rest, which results in a lower BP value [15] and is recommended in recent guidelines [7, 16, 17]. Furthermore, the use of automated devices for office BP measurement has become increasingly common in recent clinical practice [18]. The essential difference between the initially defined AOBP [13, 14] and conventionally measured office BP therefore comes down to the difference in whether the medical staff is unattended or attended during the measurement. Controversial findings regarding the difference in the unattended office BP and HBP have been reported [19, 20], and whether unattended office BP can be treated as an alternative to HBP or as just a variant of office BP measurements by automated devices also remains unclear. We, therefore, conducted a multicenter clinical study in Japan to compare the HBP, unattended office BP, and conventionally measured attended office BP assessed using automated devices among patients with hypertension.

Methods

Study population

The present Comparison of Self-measured home, Automated unattended office and Conventional attended office blood pressure (COSAC) study was part of a multicenter clinical study comparing the self-measured HBP, unattended office BP, and conventionally measured attended office BP using automated devices among patients with hypertension. The entire study project was designed by the working group of the Japanese Society of Hypertension (see “Acknowledgements”). The study was conducted at Miyakawa Clinic of Internal Medicine and Pediatrics (Yokohama, Japan), Katsuya Clinic (Amagasaki, Japan), and Yokohama Sotetsu bldg. Clinic of Internal Medicine (Yokohama, Japan) where the working group members (MM, TK, and HM, respectively) were administered. The study protocol complies with the recent Declaration of Helsinki for the Investigation of Human Patients [21] and is registered with the UMIN Clinical Trial Registry as an observational study (UMIN000026721; <http://www.umin.ac.jp/ctr>). The institutional review board of the University of the Ryukyus approved the study protocol (#1042 on February 2, 2017), and all study participants provided their informed consent.

Eligible patients were those with essential hypertension and ≥ 50 years of age who were able to measure and record their HBP by themselves regularly. Patients who declined to participate in the study or were considered ineligible by their doctors were excluded. Because no similar clinical study comparing these 3 BP values had been conducted, we arbitrarily set the target population size to 300, with doctors at the 3 clinics recruiting 100 patients each. Ultimately, 308 patients across all 3 clinics completed the initial assessment.

BP measurement

HBP values were measured over 5 days just before the clinic visit for the general assessment with office BP measurements. At the clinic visit, study doctors measured the conventional attended office BP before measurement of the unattended office BP to prevent unexpected effects of the unattended office BP measurement on the conventional office BP values. The study patients were asked to maintain the same antihypertensive medications during the HBP and office BP measurements.

The doctors instructed patients on HBP measurement in accordance with the JSH 2014 Guidelines [7] and confirmed the effective use of the popular upper-arm cuff-oscillometric BP monitor. Patients were asked to measure their HBP in the sitting position twice every morning after at least 2 min of rest. They had to obtain these measurements within 1 h of waking, before breakfast, and before taking antihypertensive medication. They were also asked to measure their HBP twice every evening just before going to bed.

Unattended office BP was captured using the validated [22] upper-arm cuff-oscillometric Omron HEM-907 (Omron Healthcare Co. Ltd., Kyoto, Japan) automated sphygmomanometer, which was also used in SPRINT [10–12]. Trained medical staff in each clinic set the monitor to automatically wait 5 min and then activate to measure the BP three times consecutively at 1-min intervals. Once the staff left the examination room after attaching a proper-size arm-cuff to the study patient, the patient sat alone in a back-supported chair for the resting period, after which the measurement was automatically performed. Throughout the process, the patient was not completing questionnaires, talking, or texting. This measurement procedure fully complied with the most stringent unattended BP measurement conditions used in SPRINT—patients were left alone during the antecedent rest as well as the BP measurements [12].

Conventional attended office BP was measured in accordance with the JSH 2014 Guidelines [7]. All three study doctors used the same Omron HEM-907 automated sphygmomanometer and directly measured the BPs of their patients in the consultation room. After a few minutes of

rest, they measured the office BP twice at the Katsuya Clinic and Yokohama Sotetsu bldg. Clinic with a 1- to 2-min interval, but only once at Miyakawa Clinic, while maintaining the arm-cuff position at the level of the heart in a seated position.

Other measurements and quality control

We used the questionnaire to obtain information on each patient's medical history and related conditions. We asked the doctors to define each patient's complications according to the common definition used in Japan, e.g., diabetes mellitus was determined by the use of antidiabetic drugs, a fasting blood glucose concentration of ≥ 7.0 mmol/L, a random blood glucose concentration of ≥ 11.1 mmol/L, or diabetes documented in the clinic records. A history of cardiovascular disease included both nonfatal stroke and nonfatal myocardial infarction. The body mass index was the body weight in kilograms divided by the height in meters squared. The amount of antihypertensive medication in individuals was standardized using the defined daily doses (2018 version) [23], which is the assumed average maintenance dose per day for a drug used for its main indication in adults developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology System of Defined Daily Doses.

HBP measurements were recorded on paper and then collected and inspected by each study doctor. The numbers of patients who reported identical systolic/diastolic morning HBPs between 2 consecutive days were 2, 1, 0, and 1 between days 1–2, 2–3, 3–4, and 4–5, respectively, and all these readings came from different patients, indicating markedly limited, if any, reporting bias in the present study. All BP and other measurement data were then sent to the data management center at the University of the Ryukyus. The data manager (YI) independently inspected the collected data and made inquiries to the study doctors as necessary. Before and during the study period, the investigators had biannual meetings in connection with the major scientific conferences and regular monitoring at the three clinic sites to ensure the quality of the study.

Statistical analyses

We used SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) for database management and statistical analyses. The statistical significance was $\alpha < 0.05$ in 2-sided tests. All data are expressed as the mean (SD) unless otherwise stated.

For the HBP, the average morning and evening HBP values were separately analyzed because previous studies have shown that these measurements have different prognostic meanings [24, 25]. For the unattended and attended

office BP values, all of the readings were averaged for the analysis.

We performed the Kruskal–Wallis test and Fisher's exact test to compare means and proportions, respectively. Bland and Altman plots were used to examine the agreement between BP values. Pearson's correlation coefficients were calculated to determine the correlation between each BP value because BPs can be treated as a normal distribution. The correlations of the mean difference between in-office BPs and HBPs were also assessed to determine whether a white-coat effect, defined as the conventional attended office BP minus the HBP, was present in the unattended office BP. We further applied multiple linear regression models to explore independent factors associated with the mean difference between BP values. For the multivariate analysis, the following factors were included: sex, age, overweight (body mass index ≥ 25 kg/m²), current smoking and drinking status, diabetes, dyslipidemia, cardiovascular disease history, clinic sites, and defined daily doses.

Results

The clinical characteristics of the 308 eligible patients are shown in Table 1. A total of 178 (57.8%) were women, and the mean age was 71.8 years, including 244 patients (79.2%) who were ≥ 65 years old. All but 11 patients (96.4%) had their BP measured under antihypertensive drug medication. Office BPs were measured from 08:20 to 18:50 within a routine clinical practice at each site, and the median time between attended and unattended office BPs was 10 min (interquartile range: 5–15 min). Of the 308 patients, 304 measured morning HBP over 5 days, and the others performed measurements over 4 days. Evening HBPs were measured by 300 patients, of whom 299, 298, and 295 patients measured evening HBPs over 3, 4, and 5 days, respectively.

Table 2 lists the correlations between unattended and attended office BP and morning and evening HBP. Scatter plots of unattended office and morning HBPs are shown in Supplementary Fig. 1. In the systolic measurement, crude correlation coefficients did not reach 0.10 ($P > 0.11$) for the comparison of HBPs vs. office BPs, except for attended BP vs. morning HBP ($r = 0.12$; $P = 0.037$). In contrast, the measurement values of attended BP vs. unattended BP and those of morning HBP vs. evening HBP were highly correlated ($r \geq 0.73$ and ≥ 0.52 , respectively; $P < 0.0001$). The correlation coefficients of HBP vs. office BPs were approximately 0.5 ($P < 0.0001$) in diastolic measurements. Similar results were observed when we adjusted for confounders. Of note, the average 3 consecutive unattended office BP measurements ranged from 129.4 (16.5)/71.1 (12.1) mmHg to 128.2 (16.0)/69.9 (12.1) mmHg as the first

Table 1 Clinical characteristics

Variables	Total (n = 308)	Miyakawa Clinic (n = 107)	Katsuya Clinic (n = 100)	YSB Clinic (n = 101)	P
Women, n (%)	178 (57.8)	76 (71.0)	48 (48.0)	54 (53.5)	0.0019
Age, years	71.8 (10.1)	69.3 (10.5)	75.2 (8.9)	71.1 (10.2)	0.0001
Body mass index, kg m ⁻²	24.9 (3.9)	24.9 (4.2)	25.2 (3.5)	24.6 (3.9)	0.34
Current smoker, n (%)	28 (9.1)	8 (7.5)	10 (10.0)	10 (9.9)	0.80
Current habitual drinking, n (%)	132 (42.9)	37 (34.6)	42 (42.0)	53 (52.5)	0.034
Diabetes mellitus, n (%)	55 (17.9)	23 (21.5)	17 (17.0)	15 (14.9)	0.48
Dyslipidemia, n (%)	189 (61.4)	86 (80.4)	51 (51.0)	52 (51.5)	<0.0001
Previous cardiovascular disease, n (%)	15 (4.9)	2 (1.9)	13 (13.0)	0 (0)	<0.0001
Antihypertensive drug treatment, n (%)	297 (96.4)	96 (89.7)	100 (100.0)	101 (100.0)	<0.0001
Defined daily doses, unit	0.99 (0.72)	0.81 (0.60)	1.22 (0.83)	0.94 (0.65)	0.0007
<i>Unattended office measurement</i>					
Systolic blood pressure, mmHg	128.9 (15.8)	135.9 (15.3)	128.0 (15.7)	122.4 (13.3)	<0.0001
Diastolic blood pressure, mmHg	70.5 (11.9)	75.7 (12.0)	67.9 (11.3)	67.5 (10.5)	<0.0001
Pulse rate, beat per minute	72.6 (11.8)	77.2 (13.5)	67.2 (8.3)	73 (10.8)	<0.0001
<i>Attended office measurement</i>					
Systolic blood pressure, mmHg	139.3 (16.9)	144.0 (17.4)	143.3 (16.5)	130.4 (12.9)	<0.0001
Diastolic blood pressure, mmHg	74.7 (12.2)	80.6 (11.9)	72.7 (12.5)	70.5 (9.9)	<0.0001
Pulse rate, beat per minute	76.7 (12.7)	80.3 (14.8)	72.4 (9.6)	77.1 (11.9)	0.0002
<i>Morning home measurement</i>					
Systolic blood pressure, mmHg	128.0 (9.4)	125.2 (8.7)	131.0 (9.2)	128.0 (9.5)	<0.0001
Diastolic blood pressure, mmHg	75.0 (9.2)	74.3 (10.2)	74.7 (8.6)	75.9 (8.7)	0.31
Pulse rate, beat per minute	66.2 (9.1)	66.4 (9.9)	63.6 (7.2)	68.6 (9.1)	0.0005
<i>Evening home measurement</i>					
Systolic blood pressure, mmHg	123.4 (9.8)	121.2 (10.1)	124.3 (9.3)	124.9 (9.5)	0.043
Diastolic blood pressure, mmHg	70.5 (9.7)	70.3 (10.9)	69.1 (8.2)	72.2 (9.6)	0.070
Pulse rate, beat per minute	69.0 (9.2)	68.9 (9.6)	67.6 (8.8)	70.5 (8.9)	0.066

Values are shown as the number of patients (percentage), or mean (SD) for continuous variables. Definitions of each complication of the patients were reported by study clinics according to the most commonly used definition in Japan. Evening home measurements were unavailable in eight patients (one from Katsuya Clinic and seven from Yokohama Sotetsu bldg. [YSB] Clinic)

to third measurements, showing almost identical values among patients ($r \geq 0.90$).

The mean difference in the BP values between unattended and morning home measurements, attended and morning home measurements, and attended and unattended measurements were 0.9 (17.8)/−4.5 (10.5), 11.3 (18.3)/−0.3 (10.8), and 10.4 (12.0)/4.2 (6.5) mmHg, respectively, as shown in the Bland and Altman plots in Figs. 1–3. The differences between unattended and evening HBPs and attended and evening HBPs were 5.7(17.8)/−0.1(11.3) mmHg (Supplementary Fig. 2) and 16.3(19.1)/4.3(11.8) mmHg (Supplementary Fig. 3), respectively, and that between morning and evening HBP was 4.7(9.4)/4.3(6.1) mmHg (Supplementary Fig. 4). The mean differences between unattended BP and HBP and between attended BP and HBP—the white-coat effect in a narrow and broad sense, respectively—were highly correlated (morning HBP-based white-coat effects, $r = 0.78/0.81$; evening-based,

0.79/0.84; $P < 0.0001$). This finding was consistently observed when patients from the 3 clinic sites were analyzed separately ($r \geq 0.68/\geq 0.67$, $P < 0.0001$). Correlation coefficients in the Bland and Altman plots were significant when office and HBPs were assessed (Figs. 1 and 2, and Supplementary Figs. 2 and 3; $P < 0.0001$), but not when attended and unattended as well as morning and evening HBPs were assessed (Fig. 3 and Supplementary Fig. 4; $P \geq 0.080$). BPs and defined daily doses in the cross-classification of patients based on HBPs and office BPs are shown in Supplementary Table 1.

A multiple regression analysis showed that the clinic sites consistently affected the differences in the office vs. HBP values for systolic (Table 3) and diastolic (Table 4) measurements. Basic characteristics, such as sex, age, and antihypertensive treatment, represented as defined daily doses, did not markedly affect the BP changes ($P \geq 0.055$), except for age and sex concerning unattended BP vs.

Table 2 Correlations between the measurements

Variables	Unadjusted <i>r</i> (95% CI)	Adjusted <i>r</i> (95% CI)
<i>Unattended—morning home (n = 308)</i>		
Systolic blood pressure	0.07 (−0.05 to 0.18)	0.14 (0.03–0.25)*
Diastolic blood pressure	0.53 (0.45–0.61)**	0.46 (0.37–0.55)**
Pulse rate	0.57 (0.49–0.64)**	0.54 (0.46–0.62)**
<i>Unattended—evening home (n = 300)</i>		
Systolic blood pressure	0.09 (−0.02 to 0.20)	0.16 (0.04–0.27)***
Diastolic blood pressure	0.47 (0.38–0.56)**	0.40 (0.29–0.49)**
Pulse rate	0.50 (0.41–0.58)**	0.51 (0.42–0.59)**
<i>Attended—morning home (n = 308)</i>		
Systolic blood pressure	0.12 (0.01–0.23)*	0.15 (0.03–0.26)*
Diastolic blood pressure	0.53 (0.44–0.60)**	0.48 (0.38–0.56)**
Pulse rate	0.52 (0.43–0.60)**	0.50 (0.41–0.58)**
<i>Attended—evening home (n = 300)</i>		
Systolic blood pressure	0.05 (−0.06 to 0.16)	0.10 (−0.02 to 0.21)
Diastolic blood pressure	0.45 (0.35–0.53)**	0.39 (0.29–0.49)**
Pulse rate	0.44 (0.34–0.52)**	0.44 (0.34–0.53)**
<i>Attended—unattended (n = 308)</i>		
Systolic blood pressure	0.73 (0.67–0.78)**	0.72 (0.67–0.77)**
Diastolic blood pressure	0.86 (0.82–0.88)**	0.79 (0.75–0.83)**
Pulse rate	0.91 (0.89–0.93)**	0.91 (0.89–0.93)**
<i>Morning home—evening home (n = 300)</i>		
Systolic blood pressure	0.52 (0.43–0.60)**	0.52 (0.43–0.60)**
Diastolic blood pressure	0.80 (0.75–0.83)**	0.76 (0.71–0.80)**
Pulse rate	0.76 (0.71–0.81)**	0.75 (0.70–0.80)**

Values are shown as Pearson's correlation coefficient *r* (95% confidence intervals [CI]). Adjusted estimates accounted for sex, age, overweight ((body mass index ≥ 25 kg/m²), current smoking and drinking, diabetes, dyslipidemia, cardiovascular diseases history, clinic sites, and defined daily doses. Unattended and attended denote unattended office blood pressure and conventionally measured attended office blood pressure, respectively

* $P < 0.05$ was considered significantly different

** $P < 0.0001$ was considered significantly different

*** $P < 0.01$ was considered significantly different

morning HBP and attended BP vs. unattended BP in systolic measurements ($P \leq 0.050$). The results were essentially similar when we assessed evening HBP, as shown in Supplementary Tables 2 and 3. When we compared the

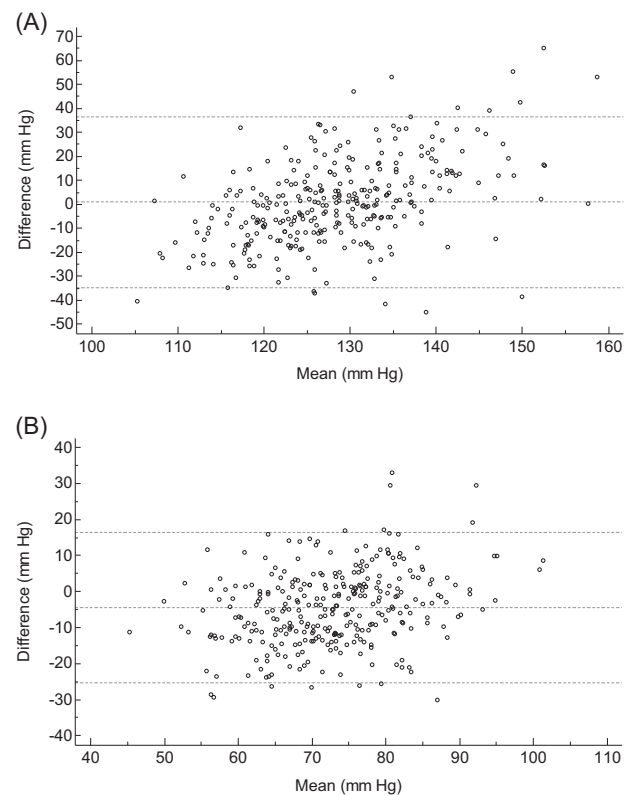


Fig. 1 Bland and Altman plots for the comparison between unattended office blood pressure and morning home blood pressure in **a** systolic and **b** diastolic measurements. Mean differences and ± 2 SD between paired measurements are represented by full and dotted lines, respectively. The correlation coefficients between the difference and the mean were 0.48 ($P < 0.0001$) for systolic and 0.29 ($P < 0.0001$) for diastolic measurements

difference in the measurements according to the prescribed timing of antihypertensive drugs, neither morning nor evening-to-bedtime prescription significantly affected the difference ($P \geq 0.21$), except for the difference between attended office and morning HBP in the systolic measurements (Supplementary Table 4; 13.8 [19.0] mmHg among patients with a morning prescription vs. 9.0 [18.0] mmHg among those with an evening-to-bedtime prescription; $P = 0.042$)

Based on the morning HBP, 87 (28.2%) patients had uncontrolled hypertension ($\geq 135/\geq 85$ mmHg). Although the average morning HBP among patients with uncontrolled hypertension was 13.7 (7.1)/9.0 (8.3) mmHg higher than that among the other 228 controlled patients ($P < 0.0001$), the intensity of antihypertensive treatment, as represented by defined daily doses, was not significantly different (1.11 [0.83] vs. 0.94 [0.66] unit, $P = 0.16$). Furthermore, the uncontrolled and controlled patients did not demonstrate substantially different office BPs (unattended BP, 131.5 (14.2)/73.0 (13.5) vs. 127.9 (16.2)/69.5 (11.1) mmHg, $P = 0.035/0.029$; attended BP, 141.1 (16.6)/77.8 (14.7) vs.

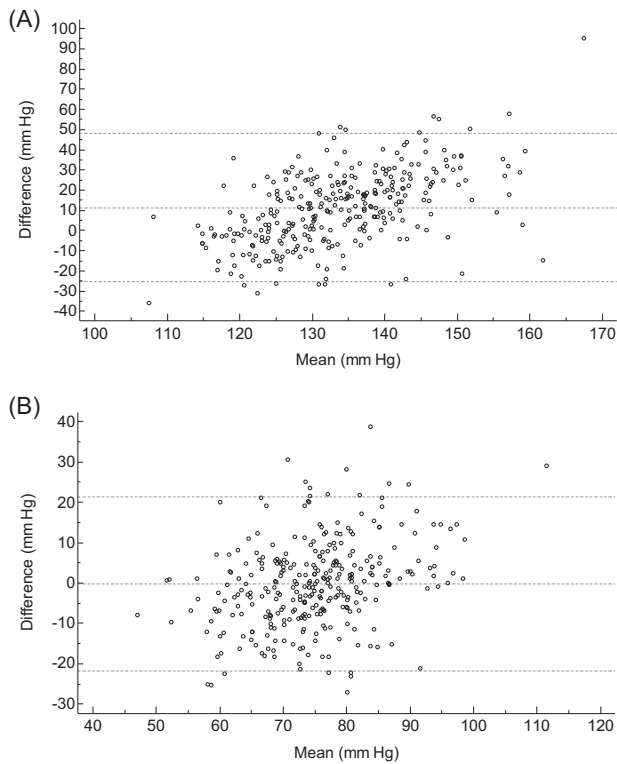


Fig. 2 Bland and Altman plots for the comparison between conventionally measured attended office blood pressure and morning home blood pressure in **a** systolic and **b** diastolic measurements. Mean differences and $\pm 2SD$ between paired measurements are represented by full and dotted lines, respectively. The correlation coefficients between the difference and the mean were 0.53 ($P < 0.0001$) for systolic and 0.32 ($P < 0.0001$) for diastolic measurements

138.6 (17.0)/73.5 (10.9) mmHg, $P = 0.18/0.026$). Similarly, 46 (15.3%) patients had uncontrolled hypertension based on their evening HBP, with a 17.6 (7.5)/13.2 (8.5) mmHg difference ($P < 0.0001$) compared with that of 254 controlled patients. However, the defined daily doses significantly differed between the uncontrolled and controlled patients (1.29 [0.92] vs. 0.93 [0.67] unit, $P = 0.0089$). The unattended office BP values in patients with uncontrolled and controlled evening hypertension were 133.8 (15.0)/74.8 (13.7) and 128.3 (15.9)/69.7 (11.5) mmHg, respectively ($P = 0.022/0.012$), and the corresponding attended BP values were 142.0 (17.6)/79.1 (15.5) and 139.2 (16.8)/74.0 (11.5) mmHg, respectively ($P = 0.27/0.031$).

Discussion

We performed the COSAC study to identify the clinical significance of AOBP officially used in SPRINT [11]—unattended office BP measured by automated devices—in comparison with HBP. Surprisingly, the unattended office BP and HBP provided essentially different information,

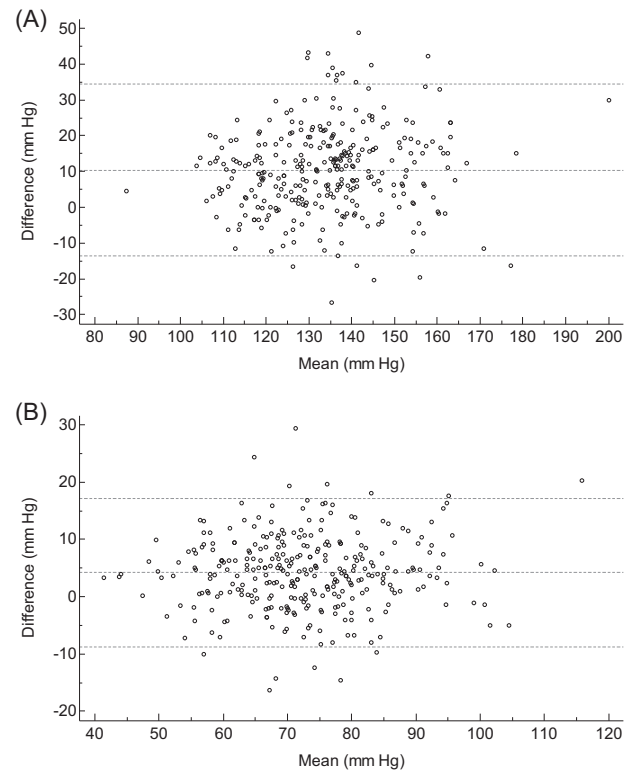


Fig. 3 Bland and Altman plots for the comparison between conventionally measured attended office blood pressure and unattended office blood pressure in **a** systolic and **b** diastolic measurements. Mean differences and $\pm 2SD$ between paired measurements are represented by full and dotted lines, respectively. The correlation coefficients between the difference and the mean were 0.10 ($P = 0.080$) for systolic and 0.055 ($P = 0.34$) for diastolic measurements

based on our findings concerning the correlation coefficients and Bland and Altman plots. However, high correlations were noted between conventional attended BP and unattended BP despite fundamental differences, suggesting that the attendance of medical staff may raise patients' BPs by an average of 11/4 mmHg. Unattended office BP might be a useful alternative to conventional attended office readings when considering the shift in the values, which might correspond to a sort of white-coat effect.

The unattended office BP measured by automated devices is also called the AOBP; however, there is some confusion regarding the definition of AOBP. AOBP was initially defined as multiple readings (three or more) [14] recorded automatically with the patient resting undisturbed in a quiet place in the absence of an observer [13, 14], but no antecedent rest time was defined. In SPRINT, the office BP was measured using the automated Omron HEM-907 cuff-oscillometric monitor [22] with a 5-min rest period before the first measurement and a 1-min interval between measurements. The SPRINT investigators later reported that 38 of the 88 SPRINT clinic sites complied with the definition of AOBP [13, 14], but staff attended measurements

Table 3 Independent factors associated with differences in the systolic blood pressure by fully adjusted multiple regression models

Variables	Unattended—Home		Attended—Home		Attended—Unattended	
	Point estimate	95% CI	Point estimate	95% CI	Point estimate	95% CI
Average blood pressure (per 1 mmHg)	0.83	(0.65–1.00)*	0.91	(0.74–1.09)*	0.08	(–0.02 to 0.17)
Women (vs. men)	–0.88	(–4.65 to 2.89)	0.83	(–2.99 to 4.66)	3.00	(0.01–5.98)*
Age (per 10 years)	–1.74	(–3.42 to –0.05)**	–1.28	(–2.99 to 0.44)	0.88	(–0.46 to 2.21)
Overweight	0.39	(–3.09 to 3.86)	0.48	(–3.05 to 4.01)	0.07	(–2.69 to 2.82)
Current smoker	2.27	(–3.63 to 8.17)	–0.48	(–6.48 to 5.53)	–4.90	(–9.58 to –0.23)*
Current habitual drinking	–4.06	(–7.70 to –0.42)*	–4.06	(–7.76 to –0.36)*	0.15	(–2.74 to 3.04)
Diabetes mellitus	3.57	(–0.79 to 7.93)	4.63	(0.20 to 9.06)*	1.71	(–1.75 to 5.17)
Dyslipidemia	2.09	(–1.46 to 5.63)	0.79	(–2.81 to 4.40)	–2.33	(–5.14 to 0.48)
Previous cardiovascular disease	1.70	(–6.27 to 9.67)	2.21	(–5.89 to 10.31)	0.83	(–5.49 to 7.15)
Katsuya Clinic (vs. Miyakawa Clinic)	–10.45	(–14.91 to –5.99)*	–6.72	(–11.26 to –2.18)***	6.94	(3.39–10.48)****
YSB Clinic (vs. Miyakawa Clinic)	–9.95	(–14.17 to –5.74)*	–9.60	(–13.88 to –5.32)*	0.72	(–2.74 to 4.17)
Defined daily doses (per unit)	–1.96	(–4.33 to 0.41)	–1.77	(–4.18 to 0.65)	0.48	(–1.39 to 2.35)

Point estimates reflect the increase in the systolic blood pressure difference per variable unit. Home denotes morning home blood pressure, and results on evening home blood pressure are shown in Supplemental Table 1. Unattended and attended denote unattended office blood pressure and conventionally measured attended office blood pressure, respectively. The variance inflation factors were ≤ 1.71 . CI confidence intervals, YSB Yokohama Sotetsu bldg.

* $P < 0.0001$ was considered significantly different

** $P < 0.05$ was considered significantly different

*** $P < 0.01$ was considered significantly different

**** $P < 0.001$ was considered significantly different

during the rest time and/or during the measurement at the other 50 sites, although the BPs measured during the trial were almost identical on cross-classification of the attended and unattended site groups. In the present study, fully conforming unattended office BP was measured as the unattended BP, and the attended office BP was measured using the same HEM-907 device but with measurements directly performed by study doctors according to the JSH 2014 guidelines [7], which recommend a few minutes of rest and 1- to 2-min intervals. Therefore, the key difference in the condition between the two in-office measurements is whether patients were alone in a separate room during the measurement. The unattended condition allows us to refine the BP information by eliminating an aspect of the white-coat effect incurred by being in the presence of medical staff.

In the present study, the mean difference between the attended and unattended office systolic BP was larger in women than in men (by 3.0 mmHg) as well as in non-smokers than in smokers (by 4.9 mmHg). These factors have been reported to enhance the white-coat effect [26, 27], implying that the fundamental differences between attended and unattended office BP can be explained in part by the white-coat effect in a narrow sense. However, the

unattended BP is measured at a clinic or in a screening setting, and the remaining portion of the white-coat effect—which can be called the clinic effect—still remains, as the circumstances are quite different from relaxing at home. Unattended BP measurements may therefore be a useful alternative to conventional office measurements [13, 28]. The currently observed high reproducibility of the three consecutive unattended BP readings in each patient ($r \geq 0.90$) also supports the positive application of the measurement. However, the prognostic significance of the unattended BP is not equivalent to the out-of-office measurements because of the inability to entirely eliminate the clinic effect during in-office measurement.

The weak association between office BPs and HBPs observed in the present study remains a matter of debate. The majority of the study patients (96.4%) received anti-hypertensive drug treatment. In the Ohasama study, correlations between conventional BP and morning HBP were stronger among untreated participants ($r = 0.55/0.50$ in systolic/diastolic measurement) than among treated patients ($r = 0.29/0.38$) [29]. Though not fully addressed, anti-hypertensive drug treatment might reduce the reliability of office BP reading, resulting in the low correlations observed among treated patients. Moreover, the time intervals

Table 4 Independent factors associated with differences in the diastolic blood pressure by multivariable-adjusted regression models

Variables	Unattended—Home		Attended— Home		Attended—Unattended	
	Point estimate	95% CI	Point estimate	95% CI	Point estimate	95% CI
Average blood pressure (per 1 mmHg)	0.23	(0.10–0.37)*	0.29	(0.16–0.43)**	0.05	(–0.02 to 0.13)
Women (vs. men)	0.53	(–1.88 to 2.94)	0.61	(–1.82 to 3.04)	0.07	(–1.60 to 1.74)
Age (per 10 years)	–0.86	(–2.14 to 0.42)	–0.09	(–1.35 to 1.17)	0.86	(–0.02 to 1.73)
Overweight	–1.07	(–3.28 to 1.14)	–0.60	(–2.83 to 1.63)	0.56	(–0.97 to 2.10)
Current smoker	2.19	(–1.59 to 5.97)	0.10	(–3.72 to 3.92)	–2.45	(–5.07 to 0.17)
Current habitual drinking	–0.36	(–2.69 to 1.98)	0.63	(–1.72 to 2.98)	1.13	(–0.49 to 2.75)
Diabetes mellitus	1.13	(–1.67 to 3.93)	2.10	(–0.71 to 4.92)	1.06	(–0.88 to 2.99)
Dyslipidemia	2.24	(–0.05 to 4.52)	1.09	(–1.22 to 3.41)	–1.38	(–2.96 to 0.20)
Previous cardiovascular disease	4.83	(–0.26 to 9.93)	5.05	(–0.09 to 10.19)	0.12	(–3.42 to 3.66)
Katsuya Clinic (vs. Miyakawa Clinic)	–6.28	(–9.14 to –3.43)**	–7.02	(–9.90 to –4.14)**	–0.69	(–2.71 to 1.33)
YSB Clinic (vs. Miyakawa Clinic)	–7.93	(–10.59 to –5.27)**	–9.87	(–12.58 to –7.16)**	–2.03	(–3.97 to –0.10)***
Defined daily doses (per unit)	–0.46	(–1.97 to 1.05)	–0.28	(–1.80 to 1.24)	0.22	(–0.83 to 1.26)

Point estimates reflect the increase in the diastolic blood pressure difference per variable unit. Home denotes morning home blood pressure, and results on evening home blood pressure are shown in Supplemental Table 2. Unattended and attended denote unattended office blood pressure and conventionally measured attended office blood pressure, respectively. The variance inflation factors were ≤ 1.76 . *CI* confidence intervals, *YSB* Yokohama Sotetsu bldg.

* $P < 0.01$ was considered significantly different

** $P < 0.0001$ was considered significantly different

*** $P < 0.05$ was considered significantly different

between office BPs vs. morning and evening HBPs varied, from at least 1 h to more than a half day. Such diverse time intervals might contribute to these lower correlations compared with the high correlations between attended and unattended office BP.

There were significant associations between the difference and the mean, i.e., correlation coefficients in the Bland and Altman plots, when office BPs vs. HBPs were assessed ($P < 0.0001$), indicating that there was a systemic proportional trend in each relationship. The 2017 ACC/AHA Guidelines [17] proposed that corresponding thresholds for hypertension based on conventional office and HBP measurement are at similar levels in the lower BP range (both 120/80 mmHg and 130/80 mmHg), but those in-office measurements were set higher than home measurements in the higher BP range (office BP corresponding to HBP; 140/90 to 135/85 mmHg, and 160/100 to 145/90 mmHg). Such discrepancies in the higher range and similarity in the lower range were based on previous reports for the distribution of office and HBP and outcome-driven operational thresholds by a participant-level meta-analysis [30]. However, no significant associations within the Bland and Altman plots were observed when unattended office BP and attended office BP were assessed ($P \geq 0.080$),

implying the similarity between unattended and attended office BP.

The consumption of office space and long measurement time reduce the feasibility of employing unattended BP measurements in clinical practice. The unattended BP reading used in the present study requires >10 min per person to obtain a few minutes for preparation and clean up, 5 min for resting before the first measurement, 3 min for resting across the intervals, and a further few minutes during cuff inflation and deflation based on the end-to-start principle, i.e., intervals are counted from the end of complete cuff deflation of the previous measurement to the start of the subsequent measurement (Table 5). Another device commonly used to measure the AOBP is the BpTRU [31] (BpTRU Medical Devices, Coquitlam, Canada; the company ceased operations in 2017), which performs six readings but averages the second to sixth readings as the default setting. Because the interval in BpTRU is based on the start-to-start principle, i.e., the interval is calculated from the start of the previous measurement to the start of the subsequent measurement (Table 5) [32], the five recorded readings with the BpTRU take as much time as three readings with other devices [32]. However, regardless of variations in measurement devices, unattended office BP

measurements would not be feasible for application in routine outpatient settings. The overall length of consultation time with a general practitioner was reported to be 10.7 (6.7) min in 6 European countries [33] and 10.1 (5.3) min according to a recent surveillance of 22 Japanese diabetes physicians in central Tokyo [34]. If we introduce unattended BP measurement to all outpatients, then we should prepare at least one extra separate room with a person in charge to manage the unattended BP measurement under the condition that the cost of the measurement is not generally reimbursed. Furthermore, we could not provide any rationale to concentrate medical resources on unattended office BP measurement based on the current study.

In 2016, Filipovský et al. [20] reported on the relationship between HBP, unattended office BP measured by the BpTRU device, and conventional office BP measured by a mercury sphygmomanometer among 353 patients with hypertension (women 49.6%, mean age 61.4 years, under antihypertensive drug treatment 97.5%) at a single clinic site. Two or more antihypertensive drugs were prescribed for 82% of patients. Although patients rested 5 min before the first measurement, the mean unattended office BP values dropped from 135/79 mmHg at the second measurement to 129/77 mmHg at the 6th measurement. In contrast to the corresponding level in our study, the unattended office BP level was significantly lower than both the attended office BP determined by a mercury sphygmomanometer and the HBP by 15.0 (13.8)/8.0 (7.3) mmHg ($n = 353$) and 10.0 (17.9)/4.2 (8.3) mmHg ($n = 114$), respectively, with large individual differences. However, Bauer and colleagues reported that unattended office BP measured by the Omron HEM-907 device was significantly higher than the HBP by 8.7 (17.3)/1.7 (10.2) mmHg among 107 patients with hypertension (women 45.8%, mean age 69.5 years, under antihypertensive drug treatment 90.7%) from 4 clinic sites who had attended these offices for at least 1 year [19]. The HBP measurement conditions in those studies [19, 20] were similar to our own, as more than 90% of patients took antihypertensive drugs, and before visits to a clinic, patients measured their HBP for 7 days [19] or for 7 days with the exclusion of the first-day values (both morning and evening) [20] using their own HBP measurement devices. Of note, 33.6% of German patients used a wrist device [19], while all other patients [19, 20] as well as our own used an upper-arm cuff device. In addition to large differences in average BP between the unattended office BP and HBP among these studies, a large individual difference was commonly observed, supporting our finding that unattended BP could not be used as an alternative to HBP.

Although all clinic sites sufficiently followed the definition of AOBP [13, 14] for the measurement of unattended office BP, the environment of each room differed. For

Table 5 Office blood pressure measurement conditions using an automated device

Items	Unattended BP in the present study [11, 12]	JSH 2014 [7]	ACC/AHA 2017 [17]	ESC/ESH 2018 [16]	Unattended BP by BpTRU [30]
<i>Before the measurement</i>					
Rest period	5 min	A few min	>5 min	5 min	N/A
Medical staff	Absent	N/A (Present)	N/A (Present)	N/A (Present)	N/A
Inspection the measurement	No; instructed before the start, and left alone	All	All	All	1st time only
<i>During the measurement</i>					
Interval	1 min (end to start)	1–2 min	1–2 min	1–2 min	1–2 min (start to start)
Medical staff	Absent	N/A (Present)	N/A (Present)	N/A (Present)	Absent
Measurement times	3	≥2	≥2	3; additionally 1 when the 1st and 2nd readings differ by >10 mmHg	6
Average the readings	All	2 readings with ≤5 mmHg difference	≥2 readings obtained on ≥2 occasions	The last 2 readings	Readings on 2–6 measurement

Conditions are applicable for measurements using an automated device. The present study compared the unattended office blood pressure (BP), which was also used in the Systolic Blood Pressure Intervention Trial (SPRINT) [11, 12], the conventionally measured attended office blood pressure, obtained according to the Japanese Society of Hypertension (JSH) 2014 Guidelines [7], and the self-measured home BP. Unattended BP by BpTRU is the default settings of the device. ACC/AHA 2017 and ESC/ESH 2018 denote the 2017 American College of Cardiology/American Heart Association Guidelines and the 2018 European Society of Cardiology/European Society of Hypertension Guidelines, respectively

instance, unattended BP was measured in a treatment room for an intravenous drip partitioned by a curtain, in a bedroom for echocardiography with relaxing music, and in a fully isolated X-ray room at Miyakawa Clinic, Katsuya Clinic, and Yokohama Sotetsu bldg. Clinic, respectively. It is unclear how these different conditions directly affected the BP differences; nevertheless, it is likely that environmental factors play a major role in the differences, more so than the classic confounding factors shown in Tables 3 and 4. In addition to the aforementioned clinic effect, we should pay attention to differences in the measurement environment among clinics, even for the unattended measurement of office BP using automated devices.

The present study must be interpreted within the context of potential limitations. First, the cross-sectional design of the analysis limits causal inferences for the associations found. We were unable to assess the long-term trends or reproducibility in the differences between the various types of BP information. Second, the study patients used their own oscillometric devices that used different algorithms to compute systolic and diastolic BP. However, all devices for HBP measurements available in Japan have been manufactured in accordance with the JIS (Japanese Industrial Standard) and marketed under the certification of private third-party organizations commissioned by the Pharmaceutical and Medical Device Agency (PMDA). The current protocols for testing of the BP measurement accuracy of automated sphygmomanometers, used upon certification, include the International Protocol of the European Society of Hypertension (ESH-IP) 2010 [35] and the ISO81060-2 (2013) provided by the International Standardization Organization (ISO) [36]. Moreover, we included patients who measured their HBP regularly before the study, and all clinic staff took part in the Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) trial that proved the feasibility of long-term antihypertensive treatment guided by HBP [37]. Instruction concerning the self-measurement of HBP and HBP-based clinical practice were therefore reliably performed in accordance with the recommendation by the JSH 2014 Guidelines [7]. Nevertheless, the diverse range of available HBP devices may introduce some imprecision to BP measurement at home, and the self-reporting of HBP measurement may increase the imprecision of data, though double-checked at the clinic sites and data management center. Third, the time periods of the three BP measurements were not consistent. As morning HBP was measured within one hour of waking and as evening HBP was measured just before going to bed, the actual measurement time of HBPs depended on the lifestyle of each patient. Office BPs were also measured in various time zones, although attended and unattended office BPs were sequentially captured. Finally, we did not collect data on the

socioeconomic status of patients in the present study, which calls for further investigation.

In conclusion, although the average HBP and unattended office BP values were similar, the difference in the BP of each patient varied markedly. Indeed, the systolic home and unattended office BP showed almost no correlation, whereas the unattended office BP and conventional attended office BP were moderately to highly correlated, suggesting that the unattended BP can be interpreted to resemble the attended BP value but with more stable information [13, 28]; nevertheless, unattended office BP cannot replace HBP measurement. This latter finding is comparable to those in other studies reporting a low within-participant agreement between unattended office BP and ambulatory BP monitoring [13, 28, 38]. Furthermore, a recent meta-analysis [39] demonstrated significant heterogeneity ($P < 0.001$) between AOBP (in some studies, medical staff supervised patients during rest or BP recordings) and ambulatory BP monitoring among 19 studies. Even if the utility of AOBP is confirmed and its definition is established, some degree of white-coat effect, such as a clinic effect, will still affect such in-office readings, regardless of the direct presence of staff. HBP should therefore be prioritized, at least to a similar degree as ambulatory monitoring, in the diagnosis and treatment of hypertension [7, 40].

Acknowledgements This study is supported solely by the Japanese Society of Hypertension.

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Compliance with ethical standards

Conflict of interest KA, TO, and KK received the research support from Omron Healthcare. NH received honoraria and/or fees for the promotional materials from Astellas Pharma, Bayer Yakuhin, Mochida Pharmaceutical, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Daiichi Sankyo, and Sumitomo Dainippon Pharma, and received research funding from Teijin Pharma, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Shionogi, Astellas Pharma, Takeda Pharmaceutical, Otsuka Pharmaceutical, Asahikawa Rehabilitation Hospital, Genseikai Group, Kyokuhoukai Asahikawa Sanai Hospital, Enzankai Group, Kitasaito

Hospital, Medical Corporation Kaiseikai Onishi Hospital, and Hokkaido Welfare Federation of Agricultural Cooperatives. Remaining authors declare no conflicts of interest.

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