Sleep Blood Pressure Self-Measured at Home as a Novel Determinant of Organ Damage: Japan Morning Surge Home Blood Pressure (J-HOP) Study

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To study whether sleep blood pressure (BP) self-measured at home is associated with organ damage, the authors analyzed the data of 2562 participants in the J-HOP study who self-measured sleep BP using a home BP monitoring (HBPM) device, three times during sleep (2 AM, 3 AM, 4 AM), as well as the home morning and evening BPs. The mean sleep home systolic BPs (SBPs) were all correlated with urinary albumin/creatinine ratio (UACR), left ventricular mass index (LVMI), brachial-ankle pulse wave velocity (baPWV), maximum carotid intima-media thickness, and plasma N-terminal pro-hormone pro–brain-type natriuretic peptide (NTproBNP) (all $P<.001$). After controlling for clinic SBP and home morning and evening SBPs, associations of home sleep SBP with UACR, LVMI, and baPWV remained significant (all $P<.008$). Even in patients with home morning BP <135/85 mm Hg, 27% exhibited masked nocturnal hypertension with home sleep SBP ≥120 mm Hg and had higher UACR and NTproBNP. Masked nocturnal hypertension, which is associated with advanced organ damage, remains unrecognized by conventional HBPM. *J Clin Hypertens (Greenwich)*. 2015; 17:340–348. © 2015 Wiley Periodicals, Inc.

Recent population-based and clinical studies using ambulatory blood pressure (BP) monitoring (ABPM) demonstrate that sleep BP is a better predictor of cardiovascular disease than awake BP.[1–3] Nocturnal hypertension with higher sleep BP, and a nondipper/riser pattern with higher sleep BP than awake BP (even they are normotensive), are reported to constitute risks for hypertensive target organ damage and subsequent cardiovascular events.[4–8]

ABPM has historically been the gold standard for measuring sleep BP. Recently, however, self-measured home BP monitoring (HBPM) was introduced to measure sleep BP at home.[9] In the first-ever study of sleep BP using HBPM, BP was measured once at 2 AM automatically.[10] We recently developed an HBPM device that automatically measures sleep home BP (HBP) 20 times with data memory (Medinote; Omron Healthcare Inc., Kyoto, Japan). We showed that the sleep HBP level measured using the Medinote device was almost identical to the sleep BP level measured by ABPM, and both sleep BPs measured by HBPM and ABPM were similarly correlated with hypertensive target organ damage.[11] Another study also demonstrated that HBPM was well accepted for the assessment of nocturnal BP and the detection of nondipping status.[12]

To verify the hypothesis that sleep HBP is worth monitoring in addition to conventional HBPM in the morning (morning HBP) and in the evening (evening HBP), we studied the associations of sleep HBP and target organ damage. For this purpose, we obtained data for 2562 participants of the Japan Morning Surge Home Blood Pressure (J-HOP) study. The J-HOP study is the largest nationwide HBP cohort and employs the same HBP monitoring device and method as used in the present study: self-measurement of sleep HBP using the Medinote three times during sleep (2 AM, 3 AM, 4 AM), as well as three times in the morning and three times in the evening for 14 days.

METHODS

The recruitment of the study patients of the J-HOP study was consecutively conducted from January 2005 to May 2012 by 75 doctors at 71 institutions (45 primary practices, 22 hospital-based outpatient clinics, and four specialized university hospitals) throughout Japan. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan, approved the protocol. The study protocol was registered on a clinical trials registration site (University Hospital Medical Information Network

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Clinical Trials Registry: #UMIN000000894). Written informed consent was obtained from all patients who enrolled in the study.

Study Subjects

Between January 2005 and May 2012, we enrolled 4310 ambulatory outpatients with one or more of the following cardiovascular risks: hypertension, hyperlipidemia, diabetes (fasting blood sugar ≥126 mg/dL, receiving an antidiabetic drug), glucose intolerance, metabolic syndrome, chronic kidney disease (estimated glomerular filtration rate <60 mL), history of cardiovascular disease (coronary artery disease, stroke, aortic dissection, peripheral artery disease, congestive heart failure), atrial fibrillation, current smoking, chronic obstructive pulmonary disease, and sleep apnea syndrome. We excluded patients who had malignancy or chronic inflammatory disease. The time interval of HBPM and the assessment of organ damage was <3 months.

BP Measurements

HBP measurement was performed using a validated cuff oscillometric device (HEM-5001; Medinote; Omron Healthcare Co., Ltd)[11] according to hypertension guidelines for the management of hypertension.[13–15] This self-measured HBPM automatically makes three measurements at 15-second intervals on each occasion. The device can be set at bedtime to measure BP during sleep, and all recorded BP parameters are stored in its memory. This new computerized HBPM device automatically stores BP data separately measured in the morning, the evening, and during sleep.

We asked study patients to measure their morning HBP (measured after awakening and before breakfast and taking antihypertensive medication) and evening HBP (measured before taking antihypertensive medication and going to bed) in a sitting position for a 2-week period. All HBP data of the HBPM device were downloaded into a computer and sent to the study control center (Jichi Medical University, Tochigi, Japan). After exclusion of the data from the first day, the averages of all HBPs measured three times in the morning (morning HBP) and three times in the evening (evening HBP) for 13 days (78 readings in total) were separately calculated by the study coordinator, who was blinded to the clinical characteristics of the study participants.

In addition, those participants who agreed to do so (n=2562, or 59% of the total sample) also measured their sleep HBP on at least 1 day within the 2 weeks. Sleep HBP measurements were made only once at each of three preset times (2 AM, 3 AM, and 4 AM), and sleep HBPs were defined as the average of all sleep BPs measured.

Clinic BP was measured at local medical centers using the same HBP device and cuff used for HBP measurement after the patients had been seated for 2 minutes and was calculated as the mean of three consecutive measurements. We generally used cuffs with rubber bags 13 cm wide and 22- to 32-cm long, or 32- to 42-cm long in the case of patients with a large upper arm; this choice was left to the physicians who measured the clinic BP.

Echocardiographic and Ultrasonographic Measurements of the Carotid Artery and Pulse Wave Velocity

Echocardiography was performed at each participating institute. Two-dimensional M-mode or B-mode images were obtained using an ultrasound machine according to the guidelines of the American Society of Echocardiology. Left ventricular (LV) mass (LVM) was obtained using the formula validated by the American Society of Echocardiology: LVM=0.8 (1.04 ([LVIDD + PWTD + IVSTD]^3−[LVIDD]^3))+0.6 g, where IVSTD is the diastolic interventricular septal diameter, LVIDD is the diastolic LV dimension, and PWTD is the diastolic posterior wall diameter. The LVM index (LVMI) was calculated as LVM/body surface area, where IVSd is the interventricular septum thickness at the end of diastole, PWd is the posterior wall thickness at the end of diastole, and LVDd is the LV internal dimension at the end of diastole. Carotid intima-media thickness (IMT) was assessed for the right and left common carotid artery using a B-mode ultrasound scanner at each participating institute. Carotid IMT was measured at three points proximal to the bilateral carotid bulbus (far wall) in 10-mm segments at end-diastole and always in plaque-free segments. If plaque existed at the IMT measuring point, an appropriate adjacent portion was chosen. The mean of the right and left maximum carotid IMT (six points in total) was used in the analysis (MaxIMT). The brachial-ankle PWV (baPWV) was measured by using the volume plethysmographic method with previously validated equipment (form PWV/ABI; Omron Healthcare Co., Ltd). We used the mean of right and left baPWV values for the analysis.

Biomarker Assays

Blood and spot urine samples were collected in the morning in a fasting state at enrollment and at the end of the study. The blood samples were centrifuged at 3000 ×*g* for 15 minutes at room temperature. Plasma/serum samples after separation and urine samples were stored at 4°C in refrigerated containers and sent to a commercial laboratory (SRL Inc., Tokyo, Japan) within 24 hours. Serum samples after separation were also stored at −80°C in a refrigerator. All assays were performed within 24 hours of sample collection at this single laboratory center.

The urinary albumin level was measured using a turbidimetric immunoassay (SRL Inc.) and expressed as UACR (mg/gCr). Both serum and urine creatinine were measured by enzymatic assay. Using the stored serum samples, N-terminal pro–brain-type natriuretic peptide (NTproBNP) was measured as previously described, and high-sensitivity cardiac troponin T (hs-cTnT) levels were measured using a highly sensitive assay on an automated platform (Elecsys-2010 Troponin T hs

STAT; Roche Diagnostics, Mannheim, Germany K.K.), with a lower detection limit of 0.003 ng/mL and a reported 99th percentile value in apparently healthy individuals of 0.014 ng/mL.

The intracoefficients/intercoefficients of variation were 1.93%/3.13% for NTproBNP, 2.02%/3.02% for hs-cTnT, and 1.30%/1.85% for urinary albumin assay.

Statistical Analysis

All analyses were performed in the 2562 patients. We included patients with atrial fibrillation, and data were expressed as means (±standard deviation [SD]) or percentages. When we excluded patients with atrial fibrillation (4.1%), all the results were essentially the same. Because the distributions of UACR, hs-cTnT, and NTproBNP were highly skewed, they were log-transformed before statistical analysis and expressed as the geometric mean (±SD). Values of hs-cTnT <0.003 ng/mL (detection limit) were assigned as 0.0015 ng/mL. The chi-square test was used to evaluate differences in prevalence rates. Unpaired *t* tests were used for comparison of the mean values between two groups. Correlations among variables were analyzed using Pearson's correlation coefficient. To investigate whether lowest or highest sleep BP provides a better index of organ damages, linear regression analysis was performed, and the correlation coefficients were compared after Fisher's *z* transformation. Multiple regression analysis of biomarkers (dependent variables) was performed using BP parameters as independent variables after controlling for age, sex, body mass index, antihypertensive drug use, evening or bedtime dosing of antihypertensive drug, sleep duration, and clinic, morning, evening home SBPs. Variance inflation factors were calculated to examine the possible existence of substantial multicollinearity among the BP measurements, and values >3.0 were considered to indicate collinearity. Associations/differences with a *P* value <.05 (two-tailed) were considered to be statistically significant. All statistical analyses were performed with SPSS version 11 software (IBM, Armonk, NY).

RESULTS

Patient Characteristics

The age, BP level, and degree of target organ damage were only slightly lower in the sleep BP analysis group (n=2562) than in the group of all J-HOP study patients (n=4310) (Table I). The average number of BP readings was 73±15 for morning and evening HBP and 18±13 for sleep HBP. The average of the number of home sleep BP readings was the same (6.14±4.50 for 2 AM, 6.11±4.50 for 3 AM, and 6.03±4.50 for 4 AM; not significant). In the sleep BP analysis group, the mean clinic SBP, morning home SBP, and home sleep SBP levels were 140 mm Hg, 136 mm Hg, and 121 mm Hg, respectively. These are near the threshold of each SBP for defining uncontrolled hypertension (140 mm Hg, 135 mm Hg, and 120 mm Hg), suggesting that almost

TABLE I. Baseline Characteristics of Study Patients

	All J-HOP Study Patients (n=4310)	Sleep BP Analysis Group (n=2562)
Age, y	64.8±10.9	63.3±10.3[a]
Male, %	47.0	49.1[a]
Body mass index, kg/m^2	24.3±3.5	24.4±3.5
Waist/hip ratio	0.90±0.07	0.89±0.07
Alcohol, %	28.0	28.5[b]
Smoking, %	12.0	11.8
Dyslipidemia, %	40.7	43.2[a]
Diabetes, %	23.5	24.1
History, %		
Angina	7.2	7.3
Myocardial infarction	3.9	4.4[b]
Aortic dissection	0.7	0.8
Stroke	4.1	3.9
Congestive heart failure	1.7	1.8
Peripheral artery disease	1.0	0.8
Atrial fibrillation	3.7	4.1
Sleep apnea syndrome	3.3	4.2
Sleep duration, h	7.1±1.2	7.0±1.1[a]
eGFR<60 mL/min/1.73 m^2, %	20.4	20.6
Antihypertensive drug, %	79.1	82.5[a]
Calcium antagonist	50.8	51.3
ACE inhibitor	6.6	6.4
ARBs	51.8	51.9
β-Blocker	13.7	15.4
α-Blocker	5.0	5.1
Diuretics	26.1	28.7[a]
Aldosterone blocker	2.2	2.4
Evening or bedtime dosing of antihypertensive drug, %	27.7	29.0[b]
Statin, %	23.6	23.7
Aspirin, %	15.1	17.4[a]
Clinic SBP, mm Hg	141.3±16.5	140.0±15.3[a]
Clinic DBP, mm Hg	81.2±10.6	81.8±10.2[a]
Home morning SBP, mm Hg	138.4±15.9	136.4±14.7[a]
Home morning DBP, mm Hg	79.1±10.0	79.3±9.6
Home evening SBP, mm Hg	130.1±15.0	128.9±14.3[a]
Home evening DBP, mm Hg	72.7±9.7	72.9±9.3
UACR, mg/gCr	13.2 (7.2, 30.8)	12.1 (6.9, 27.5)[a]
LVMI, g/m^2	100±27.9	97.8±26.3[a]
baPWV, cm/s	1675±352	1630±320[a]

TABLE I. Baseline Characteristics of Study Patients (Continued)

	All J-HOP Study Patients (n=4310)	Sleep BP Analysis Group (n=2562)
MaxIMT, mm	1.05±0.45	1.08±0.48[a]
NTproBNP, pg/mL	50.6 (25.6, 97.8)	45.9 (22.9, 88.2)[a]
hs-cTnT, ng/mL	0.003 (0.003, 0.007)	0.003 (0.003, 0.006)[a]

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; baPWV, brachial-ankle pulse wave velocity (n=1489); DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T (n=2289); LVMI, left ventricular mass index (n=1092); MaxIMT, maximum carotid intima-media thickness (n=828); NTproBNP, N-terminal pro–brain-type natriuretic peptide (number of patients included in the sleep blood prssure analysis: n=2292); SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio (n=2554). Data are presented as mean±standard deviation, median (25%, 75%), or percentage. [a]*P*<.001 vs the patients excluded from the sleep blood pressure analysis. [b]*P*<.05.

half of the study patients were uncontrolled above these thresholds.

Clinic BP and HBP Levels

There was no difference between the sleep home SBP levels at 2 AM and 3 AM, while that at 4 AM was slightly higher by 1.5 mm Hg (*P*<.001) (Figure 1). Sleep diastolic BP (DBP) was also slightly increased by 1.6 mm Hg between the 2 AM and 4 AM measurements.

Distributions of Sleep HBPs

Figure 2A and 2B show the distribution of sleep HSBP (average of the sleep SBPs at 2 AM, 3 AM, and 4 AM) of the sleep BP analysis group. Among these patients, 49% and 47% exhibited uncontrolled hypertension above the threshold for sleep home SBP and DBP (120/70 mm Hg), respectively.

Association with Covariates

Home sleep SBP was positively correlated with age, use of diuretics, and clinic and home morning and evening SBPs even in the subgroup with well-controlled morning BP (all, *P*<.001) (Table S1).

Association with Target Organ Damage

The average (Figure 3), the highest, and the lowest sleep home SBPs were significantly correlated with all six measures of target organ damage (UACR, LVMI, baPWV, MaxIMT, plasma NTproBNP, hs-cTnT), while sleep home DBP was correlated only with UACR (Table II). There was no significant difference between lowest and highest sleep SBP in a comparison of the correlation coefficients from these relationship.

We subclassified the study participants into three groups (few reading, moderate reading, frequent reading) according to the number of home sleep BP readings. The correlation coefficients of home sleep SBP with measures of organ damage were higher the higher tertile than the lower tertile (Table S2).

After controlling for clinic SBP and morning and evening home SBPs, the associations of sleep home SBP with UACR, LVMI, baPWV, NTproBNP, and hs-cTnT remained significant (Table III).

Masked Home Nocturnal Hypertension

In the subanalysis of hypertensive patients with well-controlled morning HBP <135/85 mm Hg (n=1179), 27% exhibited masked home nocturnal hypertension, defined by sleep home SBP ≥120 mm Hg, and 31%

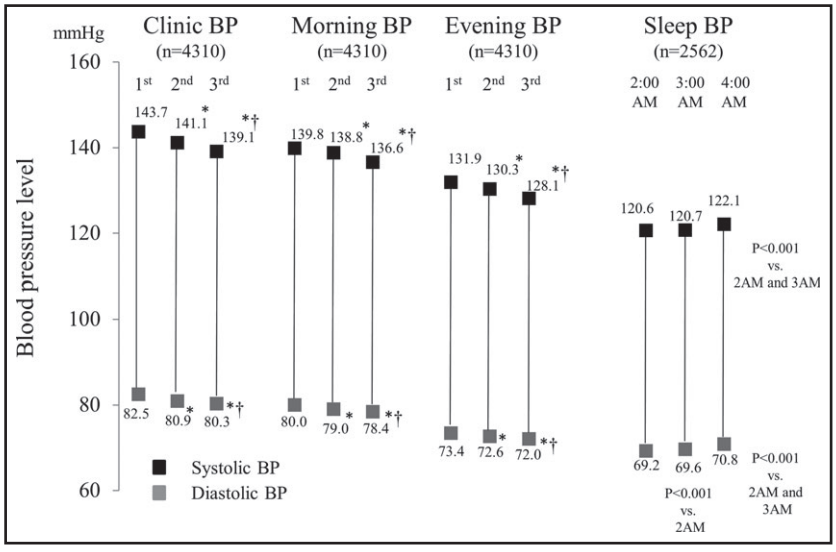

FIGURE 1. Clinic and home blood pressure (BP) level (mean) in the Japan Morning Surge Home Blood Pressure study patients. **P*<.001 vs first measurement. †*P*<.001 vs second measurement by paired *t* test. Home BPs were self-measured three times during sleep, three times in the morning, and three times in the evening, and the average for each time point is shown.

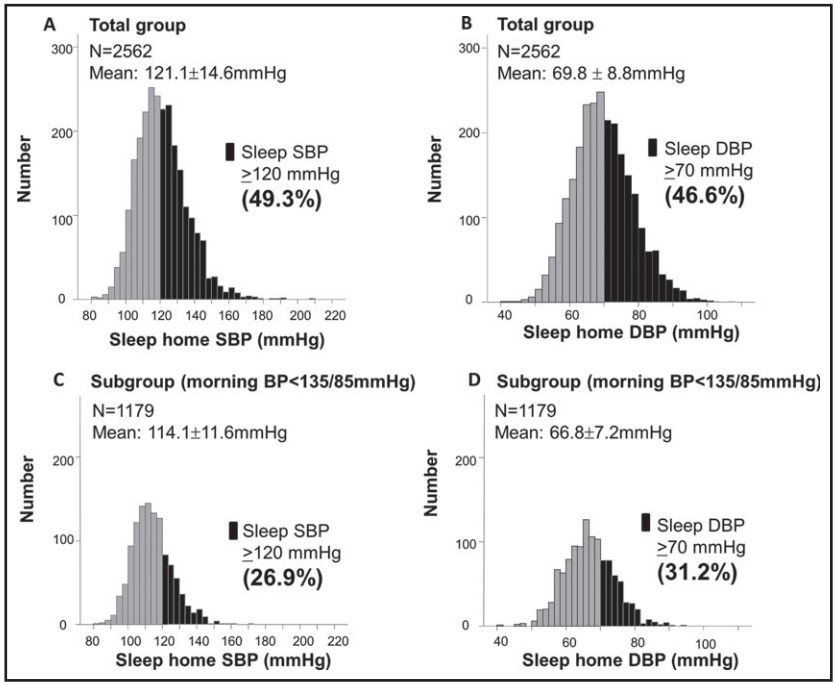

FIGURE 2. Distribution of sleep home blood pressure (BP). SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Sleep home BP is calculated as the average of three sleep home BPs measured at 2 AM, 3 AM, and 4 AM.

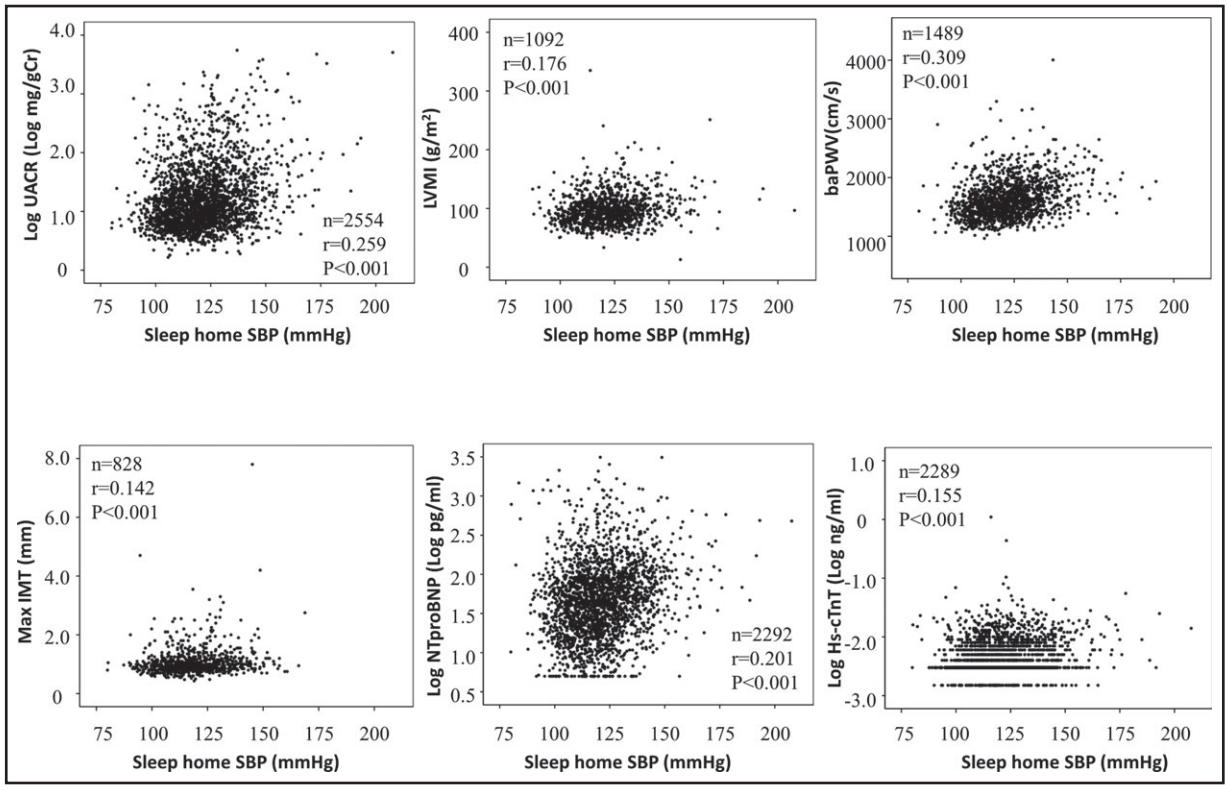

FIGURE 3. Associations of sleep home systolic blood pressure (SBP) with measures of target organ damage. UACR indicates urinary albumin/creatinine ratio; LVMI, left ventricular mass index; baPWV, brachial-ankle pulse wave velocity; MaxIMT, maximum carotid intima-media thickness; NT-proBNP, N-terminal pro–brain-type natriuretic peptide level; hs-cTnT, high-sensitivity cardiac troponin T. Sleep home SBP is calculated as the average of three sleep home blood pressures measured at 2 AM, 3 AM, and 4 AM.

TABLE II. Simple Correlations of Home Sleep Blood Pressure Parameters With Measures of Target Organ Damage

mean±SD, mm Hg		Log UACR	LVMI	baPWV	MaxIMT	Log NTproBNP	Log hs-cTnT
		R	*R*	*R*	*R*	*R*	*R*
Sleep SBP							
Average	121.1±14.6	0.26[a]	0.18[a]	0.31[a]	0.14[a]	0.20[a]	0.16[a]
2 AM	120.6±15.4	0.25[a]	0.17[a]	0.28[a]	0.13[a]	0.18[a]	0.14[a]
3 AM	120.7±15.5	0.24[a]	0.17[a]	0.29[a]	0.13[a]	0.19[a]	0.13[a]
4 AM	122.1±15.7	0.24[a]	0.16[a]	0.32[a]	0.14[a]	0.20[a]	0.15[a]
Highest	126.2±15.6	0.26[a]	0.20[a]	0.32[a]	0.12[a]	0.19[a]	0.15[a]
Lowest	116.2±14.6	0.24[a]	0.15[a]	0.27[a]	0.16[a]	0.20[a]	0.15[a]
Sleep DBP							
Average	69.8±8.8	0.12[a]	0.02	−0.01	−0.02	−0.03	−0.04[b]
2 AM	69.2±9.5	0.11[a]	0.03	−0.007	0.003	−0.04[b]	−0.05[b]
3 AM	69.6±9.3	0.10[a]	0.02	−0.02	−0.02	−0.04	−0.05[b]
4 AM	70.9±9.7	0.10[a]	0.002	0.01	−0.03	−0.03	−0.02
Highest	73.4±9.5	0.12[a]	0.04	0.01	−0.05	−0.04[b]	−0.03
Lowest	66.3±9.1	0.10[a]	−0.01	−0.03	0.01	−0.02	−0.04[b]

Abbreviations: baPWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure; hs-cTnT, high-sensitivity cardiac troponin T; LVMI, left ventricular mass index; MaxIMT, maximum carotid intima-media thickness; NTproBNP, N-terminal pro–brain-type natriuretic peptide; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin/creatinine ratio. Values are presented as Pearson's correlation coefficients (*R*). [a]*P*<.001. [b]*P*<.05.

exhibited masked home nocturnal hypertension defined by sleep home DBP ≥70 mm Hg (Figure 2C and 2D). The masked home nocturnal hypertension group (n=318) with sleep systolic HBP ≥120 mm Hg had higher UACR (11.5 [7.0–23.1 vs 8.9 [5.9–17.4] mg/gCr, *P*<.001]) and NTproBNP (49.1 [23.7–88.8] vs 36.3 [18.5–70.0] pg/mL, *P*=.003) than those with sleep systolic HBP <120 mm Hg (n=861).

Even in those with both well-controlled clinic BP <140/90 mm Hg and well-controlled morning HBP <135/85 mm Hg (n=787; average clinic, morning, and sleep HBP: 126.8±8.8/76.7±7.5 mm Hg, 123.6±7.7/74.0±6.6 mm Hg, 112.6±11.1/66.2±6.7 mm Hg, respectively), 22% exhibited masked home nocturnal hypertension defined by sleep home SBP >120 mm Hg, and 27% exhibited masked home nocturnal hypertension defined by sleep home DBP >70 mm Hg (Figure S1). The masked nocturnal hypertension group (n=173) with sleep systolic HBP >120 mm Hg had higher UACR (11.4 [7.1–21.2 vs 8.3 [5.6–16.2] mg/gCr, *P*=.002]) and NTproBNP (49.2 [26.1–88.4] vs 35.1 [17.6–69.5] pg/mL, *P*=.002) than those with sleep systolic HBP <120 mm Hg (n=614).

DISCUSSION

This study was the first to demonstrate that sleep BP measured by HBPM was associated with almost all the measures of hypertensive target organ damage independently of clinic BP and HBPs measured in the morning and in the evening, and that the prevalence of masked nocturnal hypertension with sleep SBP ≥120 mm Hg was 27% among those with well-controlled morning HBP <135/85 mm Hg in the baseline data of the largest of the nationwide HBPM cohorts that used a single high-quality automatic HBPM device with data memory and three automatic measurements of BP during the sleep period.

Sleep BP Parameters and Target Organ Damage

There was no difference between the three sleep HBP levels at 2 AM and 3 AM, while that at 4 AM was slightly higher by 1.5 mm Hg systolic and 1.6 mm Hg diastolic. However, these differences were not clinically significant. In addition, the sleep BP of ABPM was calculated as the average of the BPs during the sleep period; we also used the average of three sleep HBPs.

The average of all the sleep systolic HBPs and also the individual sleep systolic HBPs at 2 AM, 3 AM, and 4 AM were significantly correlated with all the measures of hypertensive target organ damage, such as UACR, LVMI, baPWV, MaxIMT, and the plasma levels of cardiac biomarkers (NTproBNP and hs-cTnT), while the association of sleep diastolic HBP was only found with UACR. These measures of target organ damage are the surrogate markers for predicting cardiovascular events.[16–20] Thus, a higher sleep BP level would constitute a risk for cardiovascular events independently of morning and evening BPs measured by conventional HBP measurement.

TABLE III. Multiple Linear Regression Analysis Between Sleep SBP and Target Organ Damage Additionally Adjusted for Another Blood Pressure Parameter

	Log UACR, Log mg/gCr		LVMI, g/m^2	
	Sleep SBP, mm Hg			
Additional Adjusted Factor	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	0.007 (0.006–0.009)	<.001	0.215 (0.096–0.335)	<.001
+Morning SBP	0.005 (0.004–0.007)	<.001	0.143 (0.007–0.280)	.040
+Evening SBP	0.006 (0.004–0.008)	<.001	0.172 (0.034–0.310)	.034
+Clinic SBP, morning and evening SBP	0.005 (0.003–0.007)	<.001	0.137 (−0.006 to 0.280)	.061
	baPWV, cm/s		MaxIMT, mm	
	Sleep SBP, mm Hg			
Additional Adjusted Factor	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	3.006 (2.026–3.985)	<.001	0.003 (0.001–0.006)	.011
+Morning SBP	2.394 (1.249–3.540)	<.001	0.002 (−0.001 to 0.005)	.167
+Evening SBP	1.954 (0.810–3.098)	.001	0.002 (0.000–0.005)	.105
+Clinic SBP, morning and evening SBP	1.905 (0.713–3.097)	.002	0.002 (−0.001 to 0.004)	.240
	Log NTproBNP, Log pg/mL		Log Hs-cTnT, Log ng/mL	
	Sleep SBP, mm Hg			
	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	0.005 (0.003–0.006)	<.001	0.002 (0.001–0.003)	<.001
+Morning SBP	0.004 (0.002–0.005)	<.001	0.001 (0.000–0.002)	.017
+Evening SBP	0.004 (0.003–0.006)	<.001	0.002 (0.001–0.002)	.001
+Clinic SBP, morning and evening SBP	0.004 (0.002–0.005)	<.001	0.001 (0.000–0.002)	.022

Abbreviations: baPWV, brachial-ankle pulse wave velocity; hs-cTnT, high-sensitivity cardiac troponin T; LVMI, left ventricular mass index; MaxIMT, maximum carotid intima-media thickness of carotid artery; NTproBNP, N-terminal pro–brain-type natriuretic peptide; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio. Each blood pressure parameter was added separately to the baseline regression models, which included age, sex, body mass index, use of antihypertensive drug, evening or bedtime dosing of antihypertensive drug, and sleep duration.

In addition, we also used the highest and lowest sleep HBP among the three sleep HBPs at 2 AM, 3 AM, and 4 AM as another sleep HBP parameter. The lowest sleep SBP, under the condition of the lowest sympathetic tone, may be a closer index of basal sleep BP, which is predominantly determined by the circulating volume or the structural remodeling of small resistance arteries.[9] The highest sleep BP may be a closer index of increased sympathetic tone–related sleep BP, which may be prominent in those with sleep apnea syndrome.[9,21,22] In this study, there were no significant differences in the impact of the average, the highest, and the lowest sleep BPs on target organ damage. A future study on hypertensive patients under various conditions could clarify the different impact of these sleep HBP parameters.

Association Independently of Morning BP

The association of sleep systolic HBP with measures of target organ damage (except MaxIMT) remained significant, independently not only of clinic SBP, but also of morning systolic HBP and evening systolic HBP, although morning HBP measured within 1 hour after awakening may partly be influenced by the preceding sleep BP.[23] Considering that approximately 25% of hypertensives with well-controlled morning HBP <135/85 mm Hg exhibit masked nocturnal hypertension with sleep systolic HBP >120 mm Hg, and significantly higher UACR and NTproBNP, sleep BP is worth monitoring in order to identify hypertensive patients with remaining risk during sleep, even if they are normotensive with respect to both clinic BP and morning HBP.

Recommendation of Sleep HBP-Guided Antihypertensive Medication

Sleep BP is more important in medicated than in nonmedicated hypertensive patients. The international ABPM database demonstrated that sleep BP was independently and more closely associated with cardiovascular events than awake BP in medicated hypertensives.[3] In our recent study of HBP-guided antihypertensive treatment in hypertensive patients,[24] sleep BP measured by ABPM was more closely associated with the plasma BNP level than was awake BP.[25] Even in those patients with well-controlled HBP <135/85 mm Hg, those whose sleep BP by ABPM was uncontrolled exhibited markedly higher UACR and higher plasma BNP levels.[26] These results suggest that sleep BP is a "blind spot" in current antihypertensive medication. To reduce cardiovascular events more effectively, strict 24-hour

BP, including sleep BP, is important in the management of hypertension. As a first step, recent guidelines have recommended using HBPM widely in clinical practice.[13–15] These guidelines generally recommend that HBP be measured on two occasions (in the morning and in the evening).[13–15] The measurement of sleep BP by HBPM is referred to in the guidelines, but is not conventionally recommended.[15] In this study, home sleep BP was significantly correlated with morning and evening BPs; however, home sleep BP is worth measuring, particularly in patients with diabetes mellitus, chronic kidney disease, sleep apnea syndrome, or target organ damage (those who are likely to have masked nocturnal hypertension). In this study, HBP was positively associated with age and diabetes, and "masked home nocturnal hypertension" was associated with higher UACR and NTproBNP levels. Although ABPM is the gold standard for assessing sleep BP, ABPM is inconvenient for frequent use in clinical practice. In the future, after the available data on HBPM-measured sleep BP has been expanded, HBPM could be used as an alternative device for sleep BP–guided antihypertensive medication.

Study Limitations

Various types of cardiovascular disease were included in the J-HOP study. The cause and effect relationship between sleep BP and cardiovascular disease may have varied by the nature of cardiovascular disease. Thus, by the association study using baseline data of the prospective J-HOP study, we could not refer to the cause and effect relationship between sleep HBP and measures of organ damage. Finally, the causal implication of self-measured sleep HBP will be clarified in the prospective follow-up results of the J-HOP study after adjustment for baseline cardiovascular profiles.

In addition, sleep duration and quality may modulate the association between sleep BP and organ damage. We collected the baseline data of duration and quality of sleep (presence or absence of insomnia and frequency of awakening and nocturia in each of the 14 days) in the J-HOP study, and the association between this sleep information and BPs will be studied more extensively in the future.

Finally, we should note that we did not specify the timing of the clinic BP measurement, leaving this decision to the discretion of the individual medical centers. Therefore, it might be possible that the clinic BP was underestimated because of the peak effect of the drug treatment.

CONCLUSIONS

This study first demonstrated that self-measurement of sleep HBP is feasible in a large cohort, and sleep HBP is significantly correlated with target organ damage independently of clinic BP and morning and evening HBPs. Masked nocturnal hypertension, one fourth of well-controlled morning hypertensives, remains unrecognized by conventional HBPM without sleep BP monitoring, and it was associated with advanced organ damage. Thus, sleep HBP in addition to morning HBP is worth monitoring, particularly in high-risk hypertensive patients with target organ damage. However, there are no prospective studies demonstrating that a strategy of lowering nighttime BP reduces the risk of target organ injury from hypertension. In the future, it needs to be emphasized that clinical significance of self-measured sleep BP at home should prospectively be demonstrated in the J-HOP study.

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Contributors: Kazuomi Kario is the principle investigator of the J-HOP study, supervised its conduct and data analysis, and had primary responsibility for the writing of this paper. Satoshi Hoshide, the secretary in general of the J-HOP, conducted all statistical analyses.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of sleep home blood pressure (BP) at subgroup (morning BP <135/85 mm Hg and clinic BP <140/90 mm Hg). SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Sleep home BP is calculated as the average of three sleep home BPs measured at 2 AM, 3 AM, and 4 AM.

Table S1. Simple correlations of home sleep blood pressure with covariates in the total sleep blood pressure analysis group and in subgroup well-controlled in home morning blood pressure <135/85 mm Hg.

Table S2. Simple correlations of home sleep blood pressure with measures of target organ damage in tertile of number of sleep blood pressure readings.