Original Article

Orthostatic Hypertension Detected by Self-Measured Home Blood Pressure Monitoring: A New Cardiovascular Risk Factor for Elderly Hypertensives

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Orthostatic blood pressure (BP) dysregulation is a risk factor for both falls and cardiovascular events. Self-measured BP, carried out at home, is both highly reproducible and useful for evaluating antihypertensive treatment. However, there have been a few reports on the clinical implications of orthostatic BP changes in home BP monitoring (HBPM). In the baseline examination for the Japan Morning Surge-1 Study, a multicenter randomized control trial, we evaluated 605 hypertensive outpatients who had a morning systolic BP above 135 mmHg. The plasma brain natriuretic peptide (BNP) level and urinary albumin excretion were measured. When the patients were divided into 10 groups, according to orthostatic BP change evaluated by HBPM, after adjusting for age, gender, body mass index and sitting home BP level, those in the top decile (*n*=60, orthostatic BP increase >7.8 mmHg) had a higher urinary albumin/creatinine ratio (UAR) than the lowest decile group (geometric mean [SEM range]: 209.1 [134.7–318.7] *vs.* 34.1 [20.1–56.2] mg/g creatinine [Cr], *p*=0.003) and the pooled second to ninth decile groups (*n*=485, 209.1 [134.7–318.7] *vs.* 39.7 [33.2–47.3] mg/g Cr, *p*<0.02). Additionally, patients in the top decile had a higher BNP level than the second to ninth decile groups (75.7 [55.0–103.1] *vs.* 23.6 [20.8–26.6] pg/mL, *p*=0.003). Evaluation of orthostatic hypertension at home might be a high-risk factor for cardiovascular events in hypertensive subjects with increased levels of BNP and a higher UAR, independent of the home sitting BP level. (*Hypertens Res* 2008; 31: 1509–1516)

***Key Words*: orthostatic hypertension, home blood pressure, microalbuminuria, brain natriuretic peptide**

Introduction

In elderly hypertensives, orthostatic blood pressure (BP) change is a common phenomenon. Orthostatic hypotension (OHYPO) has been shown to contribute to dizziness, falls, syncope and coronary heart disease (*1–5*). On the other hand, orthostatic hypertension (OHT), defined as an exaggerated orthostatic BP increase that occurs as the subject moves from a supine to a standing position, is reported to be associated

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with silent cerebrovascular disease and left ventricular (LV) hypertrophy (*6–10*). However, the clinical significance of OHT is not clear, as few published reports have addressed it.

The head-up tilt test is the gold standard for evaluating postural BP changes, but the reproducibility of this procedure is controversial (*11–13*). On the other hand, the evaluation of postural BP changes in an office setting may be confounded by the white-coat effect, which transiently elevates BP.

It was recently reported that self-measured home BP monitoring (HBPM) is a convenient and reproducible method for BP measurement and has a better prognostic value for cardiovascular disease than clinical BP measurement (*14–16*). HBPM-evaluated orthostatic BP change has so far not been assessed, but it might add another dimension to the measurement of home BP and its relationship to hypertensive target organ damage.

In hypertensive patients, microalbuminuria is associated with progression to atherosclerotic coronary artery disease, stroke and cardiovascular mortality (*17*, *18*). Brain-type natriuretic peptide (BNP) is reported to be mildly increased in essential hypertension and some reports have shown that the plasma BNP level is correlated with LV hypertrophy (*19*, *20*).

The Japan Morning Surge-1 (JMS-1) study is a randomized controlled trial aiming to clarify whether or not strict control by doxazosin of morning BP, measured using home BP monitoring, can decrease BNP levels and urinary albumin excretion ratios that are adjusted by the creatinine level (UAR). The detailed protocol of the JMS-1 study has been described elsewhere (*21*). In this substudy, which employed the baseline data from the JMS-1 study, we aimed to determine if HBPM-evaluated orthostatic BP change was associated with changes in UAR and BNP.

Methods

Subjects

In the baseline examination for the JMS-1 study, we selected hypertensive outpatients who had uncontrolled morning systolic blood pressure (SBP) (>135 mmHg). The patients had been maintaining a stable antihypertensive medication status for at least 3 months. We excluded patients who had arrhythmias, a history of heart failure, orthostatic hypotension with symptoms, dementia, malignancy or chronic inflammatory disease, as well as those who were taking an α- or β-blocker. Written informed consent was obtained from all patients enrolled in this study.

BP Measurements

Morning BP and evening BP were measured at home using the same device, the HEM-705IT (Omron Healthcare, Kyoto, Japan), according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (*16*). Clinic BP was measured at the office using a validated oscillometric device, the HEM-705IT (*22*), and calculated as the average of two consecutive measurements in the sitting position and the average of another two in the standing position. The subjects were instructed to place the cuff on the same arm throughout the measurements and to measure sitting BP after more than 2 min of rest in a seated position, twice per occasion, with a 15-s interval between measurements. To increase the accuracy of self-measured home BP, the subjects were instructed to practice the procedure for measuring BP in the sitting and standing positions using the same technique they had used at the clinic. The subjects then stood, remained standing for a 30-s interval, and measured their standing BP twice per occasion with a 15-s interval between the measurements. The total standing period was approximately 2 min. The subjects were instructed to keep their arms relaxed at their sides during the standing BP measurements. The cuff position was standardized to be at the heart level in both the sitting and standing positions. When standing BP was measured, both arms remained at the side of the body and the arm was supported at the level of the heart. We defined the orthostatic BP change of the clinic BP as the average of the standing SBP minus the sitting SBP.

The patients were instructed to measure the morning BP within 1 h of waking up, before breakfast and before taking antihypertensive medication, and to the measure nighttime BP just before going to bed, based on their own daily schedule. This instruction was given after each subject was given a comprehensive manual for measuring standing BP. In addition, the physicians and nurses checked the accuracy of the patients' BP measurements at the clinic. Patients were instructed to record all of the measured BP values and pulse rates and to report them to their physicians.

With regard to the home BP measurement, the BP analysis was conducted using the average of two measurements for 3 d (six readings in total) in the sitting position as well as in the standing position. We defined HBPM-evaluated orthostatic BP change as the average standing SBP measured in the morning and evening (six readings) minus the average sitting SBP (also morning and evening; six readings). With regard to the clinic BP measurement, the difference between the average of two seated readings and that of two standing readings was used as the value in the analysis. We subclassified the patients according to the extent of the orthostatic BP change based on both the clinic and home measurements as follows: patients in the top decile of orthostatic BP change were classified as the OHT group (≥11.5 mmHg in clinic SBP, >7.8 mmHg in home SBP), while those in the lowest decile of orthostatic BP change were classified as the OHYPO group (<−16.0 mmHg in clinic SBP, <−13.2 mmHg in home SBP). Patients with intermediate changes were classified as part of the orthostatic-normotension (ONT) group.

Table 1. Baseline Characteristics of the Study Patients

	OHYPO group	ONT group	OHT group	*p*-value (*F*-value)[#]
n	60	485	60	
Age (years)	73.1±8.2	69.3±9.8*	74.1±7.6††	<0.001 (9.71)
Male (%)	47	46	28†	—
Body mass index (kg/m^2)	22.8±3.7	24.2±3.3*	24.6±3.7†	0.006 (5.13)
Waist-to-hip ratio	0.90±0.08	0.91±0.08	0.92±0.11	0.355 (1.04)
Duration of hypertension (years)	8.0 (3.0–15.0)	10.0 (4.0–18.0)	12.0 (5.0–20.0)	0.399 (0.92)
Duration of hypertensive therapy (years)	4.0 (1.0–12.0)	6.0 (2.0–12.0)	8.0 (3.3–15.0)	0.215 (1.54)
Current smokers (%)	28	19	10*	—
Habitual drinkers (%)	33.3	33.6	20.0	—
Hyperlipidemia (%)	32	37	42	—
Diabetes or impaired glucose tolerance (%)	13	16	12	—
History of CAD (%)	11.7	7.2	13.3	—
History of CVD (%)	10.0	11.1	18.3	—
Number of antihypertensive drugs	1.48	1.64	1.77	0.098 (2.33)
Calcium channel blockers (%)	61.0	66.2	70.0	—
ACE inhibitors (%)	10.2	15.1	13.3	—
Angiotensin II receptor blockers (%)	57.6	58.5	62.7	—
Diuretics (%)	13.6	22.0	28.3	—
Oral drugs for diabetes mellitus (%)	8.5	8.5	10.0	—
Medication for hyperlipidemia (%)	15.3	13.7	20.0	—
Nitrates (%)	1.7	3.5	5.0	—
Anti-platelet drugs (%)	10.2	9.5	13.3	—
Clinic SBP (mmHg)	155.5±19.2	155.5±16.9	161.8±25.7†	0.039 (3.27)
Clinic DBP (mmHg)	82.3±10.1	83.6±11.6	81.5±12.1	0.298 (1.21)
Morning SBP (mmHg)	155.8±16.2	150.8±13.1*	153.7±19.4	0.017 (4.08)
Morning DBP (mmHg)	82.8±10.0	82.1±9.9	79.4±10.4	0.105 (2.26)
Evening SBP (mmHg)	141.2±15.6	139.9±15.2	140.4±19.4	0.807 (0.21)
Evening DBP (mmHg)	75.4±9.2	75.7±10.5	73.4±11.3	0.279 (1.28)
Orthostatic SBP change (mmHg)	−19.2±5.3†††	−2.2±5.1**	13.0±4.8**,†††	<0.001 (595.38)
Orthostatic PR change (mmHg)	7.0±4.6†††	5.1±3.6	6.1±3.8	<0.001 (7.91)
Creatinine (mg/dL)	0.79	0.78	0.85	0.208 (1.57)

OHYPO, orthostatic hypotension; ONT, orthostatic normotension; OHT, orthostatic hypertension; CAD, coronary artery disease; CVD, cerebrovascuar disease; ACE, angiotensin-converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate. OHYPO group is defined as the lowest decile (*i.e.*, negative change) of orthostatic home blood pressure change; ONT group is the second to ninth deciles pooled; OHT group is the top decile (*i.e.*, positive change). Data are the mean±SD and percentage or median value (25% value–75% value). *$p<0.05$, **$p<0.001$ *vs*. OHYPO group, †$p<0.05$, ††$p<0.005$, †††$p<0.001$ *vs*. ONT group are the differences among the three groups by ANOVA. [#]Overall *p*-values for three-group comparisons of means (ANOVA *F*-test) or percentage (χ^2-test).

Blood and Urine Samples

At the beginning of the study, blood and urine samples were collected in the morning from the subject in a fasting state. The urinary microalbumin level was measured using the immunoturbidimetric method (Mitsubishi Chemical Iatron, Tokyo, Japan) and expressed as the urinary albumin/creatinine ratio (UAR, mg/g creatinine [Cr]). The UAR was calculated from a morning spot urine sample. Serum and urine creatinine levels were measured by the Jaffe reaction without deproteinization and then quantified using a photometric method. All these assays were performed at Mitsubishi Biochemical Laboratory (Tokyo, Japan) and the intra- and inter-coefficients of variation for the urinary albumin assay were 1.52% and 2.48%, respectively. Plasma BNP levels were measured using high-sensitivity, noncompetitive radioimmunoassays (Shionogi, Osaka, Japan).

Statistical Analysis

We enrolled 617 patients at the beginning of the present study. After excluding 12 patients (morning SBP<135 mmHg at the time of enrollment, three patients; α-blocker or β-blocker use, two patients; duplication of enrollment, one

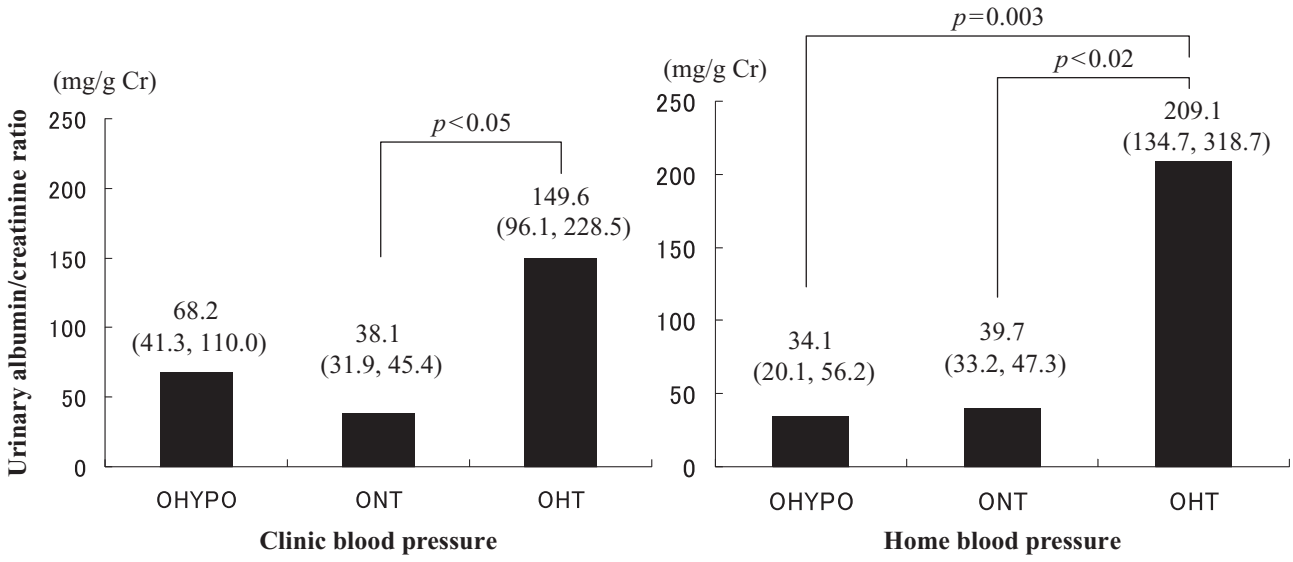

Fig. 1. *Urinary albumin/creatinine ratio and orthostatic blood pressure change. Data for urinary albumin/creatinine ratios are shown as geometric means (with the SEM range in parentheses) normalized after transformation into natural logarithms for analysis. Values were calculated from the data for three groups based on the orthostatic BP change measured in the clinic (left) and by HBPM (right). Groups were defined by deciles of BP change: the OHYPO (orthostatic hypotension) group was the decile with the most negative BP change; the OHT (orthostatic hypertension) group was the decile with the most positive change; and the ONT (orthostatic normotension) group was comprised from the eight intermediate deciles. p values show the differences between each pair and the OHYPO, ONT and OHT groups by ANCOVA, adjusting for age, gender, body mass index and sitting clinic or home systolic BP.*

patient; BP level not recorded in the standing position, six patients), statistical analyses were conducted using the remaining 605 patients.

Data are expressed as means (±SD) or percentages. As the distributions of UAR and BNP were highly skewed, these parameters were log-transformed before statistical analysis and expressed as geometric means (SEM range). The concordance of the orthostatic BP categories between clinic and home was evaluated using the κ coefficient (*23*). The relationship between morning and evening BP was analyzed by simple correlation. One-way analysis of variance (ANOVA) was performed to detect differences among groups and Tukey's honestly significant difference (HSD) test was used for multiple pairwise comparisons of means among groups. Analysis of covariance (ANCOVA) was performed to detect the groups that had differences among orthostatic BP groups after adjustment for confounding factors. The Bonferroni's test was used for multiple pairwise comparisons. The odds ratio and the 95% confidence interval (CI) of orthostatic BP groups were calculated for microalbuminuria and high-normal albuminuria by multiple logistic regression analysis.

Differences with a p-value <0.05 (two-tailed) were considered statistically significant. The software package SPSS version 11.0J (SPSS, Chicago, USA) was used for the analyses.

Results

We classified orthostatic BP change as clinic BP and as home BP. The concordance of the orthostatic BP categories in morning and evening BP was 0.44 (κ coefficient). The correlation between orthostatic BP change in the morning and in the evening was strong ($r=0.67$, $p<0.001$). Therefore, we evaluated the at-home orthostatic BP change using the average of the standing SBP measured in the morning and the evening. Table 1 shows the baseline characteristics in all patients divided by the orthostatic BP change in the home BP measurement. There were significant differences among the three groups in age, gender, clinic SBP and morning SBP. The UAR was higher in the OHT group than in any other group after adjusting for age, gender, body mass index and average sitting home SBP (Fig. 1). BNP levels were significantly higher in the OHT group than in the ONT group after adjustment for the same variables (Fig. 2). When the clinic orthostatic BP change was examined, the UAR was significantly higher in the OHT group than in the ONT group, but BNP levels showed no significant difference among the three groups. The orthostatic BP changes observed in the clinic measurements were as follows: OHYPO: −22.1±6.1 mmHg, ONT: −2.6±6.7 mmHg and OHT: 17.4±4.9 mmHg.

We conducted the analysis by separating patients with

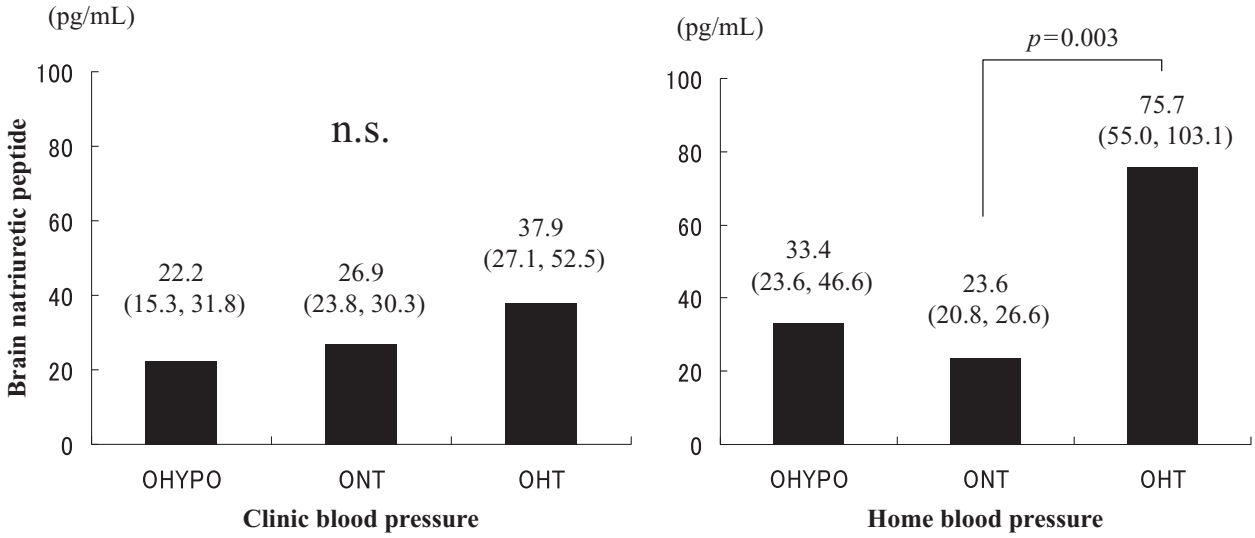

Fig. 2. *Brain natriuretic peptide and orthostatic blood pressure change. Data for BNP are shown using the same statistical analysis as in Fig. 1.*

microalbuminuria (UAR range: 30–300 mg/g Cr, $n=238$) from those without. Using a multiple logistic regression analysis, the odds ratios for microalbuminuria were estimated, as shown in Fig. 3A. In addition, we classified each of those groups into a low-normal albuminuria group, which was comprised of the lowest tertile group in terms of UAR (UAR range: 1.9–13.8 mg/g Cr, $n=202$) among all patients, and a high-normal albuminuria group (less than 30 mg/g Cr), which was comprised of patients with values higher than the lowest tertile group in terms of UAR (UAR range: 14.0–29.9 mg/g Cr, $n=165$). The odds ratios for high-normal albuminuria were estimated and are shown in Fig. 3B.

When the OHT (≥10 mmHg) and OHYPO (≤−10 mmHg) groups were defined, based on the threshold of 10 mmHg of orthostatic change in home SBP, UAR (geometric mean [SEM range]) was higher in the OHT group ($n=42$, 67.9 [55.4–83.1] mg/g Cr) than in either the OHYPO group ($n=19$, 24.5 [18.4–33.4] mg/g Cr, $p=0.04$) or the ONT group ($n=544$, 27.8 [26.2–29.3] mg/g Cr, $p<0.001$), while there were no significant differences in BNP levels among the three groups (OHYPO: 22.8 [18.7–27.9] pg/mL; ONT: 24.3 [23.4–25.2] pg/mL; OHT: 32.3 [28.3–37.0] pg/mL) after adjustment for the same variables.

In this study, we defined the seasons as follows: spring, March–May; summer, June–August; autumn, September–November; winter, December–February. We then compared clinic and home SBP levels according to the seasons. There were no significant differences in clinic or home SBPs among the seasons (data not shown).

Discussion

The main finding of this study was that the patients who showed the greatest orthostatic BP increase, as assessed by self-measured home BP monitoring, had more microalbuminuria and higher BNP levels than those showing smaller orthostatic BP increases or decreases, even after adjusting for the sitting home BP level. This is the first study to demonstrate that orthostatic BP dysregulation, assessed using self-measured home BP monitoring, is associated with potential measures of target organ damage.

Microalbuminuria, a prognostic marker for cardiovascular and renal risk in diabetic and nondiabetic subjects (*17*, *18*), was higher in hypertensive patients with OHT than in any other of the groups. BNP, which is correlated with LV mass index and relative wall thickness and is elevated particularly in those with concentric LV hypertrophy (*19*), was also higher in the OHT group than in the ONT group. Recently, the presence of low-grade albuminuria (below the threshold of microalbuminura) was reportedly associated with cardiovascular events in a community-dwelling population (*24*). That study showed that HBPM-detected OHT was a risk factor not only for microalbuminuria, but also for low-grade albuminuria. These results showed that an excess orthostatic BP increase, evaluated by HBPM, may be an important risk factor for poor cardiovascular prognosis, independent of the sitting home BP level. Previous studies have shown that OHT is associated with silent cerebral infarction or LV hypertrophy (*8–10*). However, in contrast with our study, orthostatic BP changes in previous reports were evaluated by the head-up tilt test or BP was measured in a clinical setting.

Head-up tilt testing is widely used for evaluating orthostatic BP change and for evaluating patients with unexplained syncope (*25*, *26*). However, it is difficult to use the head-up tilt test routinely in clinical practice because special equipment is needed and the procedure is time-consuming. On the

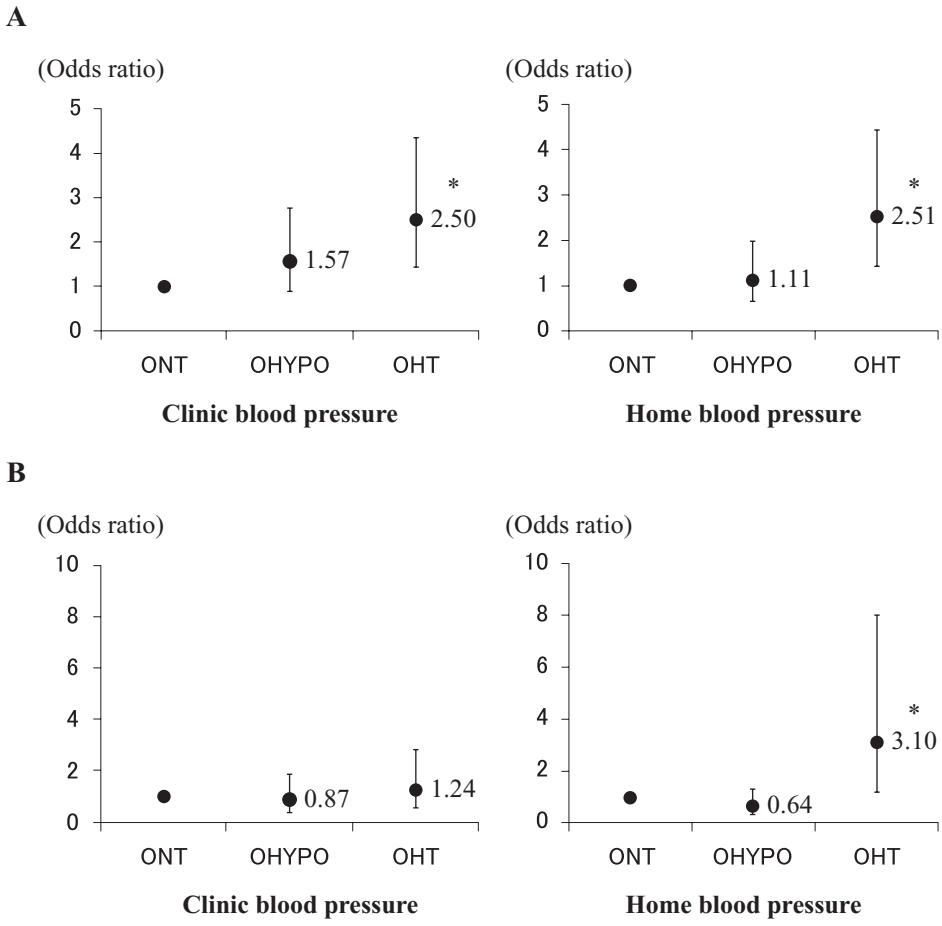

Fig. 3. *A: Microalbuminuria (≥30 mg/g Cr: n = 238) and orthostatic blood pressure change. Values were calculated from the data for three groups based on the orthostatic BP change measured in the clinic (left) and by HBPM (right). Groups were defined by deciles of BP change: the OHYPO (orthostatic hypotension) group was the decile with the most negative BP change; the OHT group was the decile with the most positive change; and the ONT (orthostatic normotension) group was comprised from the eight intermediate deciles. The odds ratio for microalbuminuria in the patients with different orthostatic BP change was adjusted for age, gender, BMI and clinic or home sitting SBP level by logistic regression analysis; *p < 0.001 vs. ONT group. B: Values were calculated from the data for three groups based on the orthostatic BP change measured in the clinic (left) and by HBPM (right). Groups were defined by deciles of BP change: the OHYPO group was the decile with the most negative BP change; the OHT group was the decile with the most positive change; and the ONT group was comprised from the eight intermediate deciles. The odds ratio for microalbuminuria in the patients with different orthostatic BP change was adjusted for age, gender, BMI and clinic or home sitting SBP level by logistic regression analysis; *p = 0.02 vs. ONT group.*

other hand, HBPM can be used to assess orthostatic BP changes without any complicated devices or procedures. Thus, the evaluation of orthostatic BP change at home might serve as a substitute for the tilt test.

The Atherosclerosis Risk in Communities (ARIC) study showed an association between orthostatic BP change and cardiovascular disease, evaluated by orthostatic BP change using clinic BP readings (*5*). The measurement of BP in a clinical setting tends to be a stressor itself and can falsely increase BP and BP reactivity through what is recognized as the white-coat effect (*27*). Recently, there have been some reports about the reproducibility and benefits of HBPM for antihypertensive treatment and about the association between home BP levels and cardiovascular disease (*14*, *28*). In the present study, the use of both clinic BP– and home BP–defined orthostatic BP change showed that UAR was significantly higher in the OHT group than in any other group, but the HBPM-defined orthostatic BP change more clearly defined the differences between the groups. On the other hand, although clinic BP–defined orthostatic BP change did not reveal a high-BNP group, BNP was significantly higher in the OHT group than in the ONT group. Therefore, the evaluation of orthostatic BP change using HBPM may be of greater value than evaluations using only changes in clinic BP.

As BNP is a less established prognostic marker in hypertensive patients, the increased BNP level observed in the present study may not be a reflection of cardiac damage, but rather of the increased LV systolic load through more frequent orthostatic BP increases in the standing position during daily activities. In addition, because our findings were derived from a cross-sectional study, it is difficult to determine whether OHT is the cause or the result of target organ damage. These results should be confirmed in a future prospective study using echocardiography for the assessment of cardiac damage.

The mechanism by which OHT is associated with high levels of BNP and UAR in this study is unclear. We previously showed that the standard deviation of awake SBP was higher in hypertensives with OHT than in orthostatic normotensives (*9*). Therefore, short-term variability accompanied by orthostatic BP change might have affected the BNP level. Frequent episodes of BP variability during daily activities may contribute to cardiac overload and future clinical events. We have also reported that OHT is associated with the augmentation index (AI), an index of wave reflection of arterial pressure (*29*). Another paper documented that the AI was correlated with the BNP level (*30*), so OHT with augmented wave reflection might increase BNP. In addition, we previously reported that the mechanism underlying OHT is associated with marked sympathetic nervous activity (*9*). Recently, it was reported that chronic kidney disease is often associated with sympathetic hyperactivity, which contributes to the development of cardiovascular and renal damage (*31*). The present study is cross-sectional, so it is not clear whether a higher UAR is a cause or a result of marked sympathetic nervous activity, but OHT with marked sympathetic nervous activity might be associated with a higher UAR.

There have been various definitions of clinical OHT in previous reports, and yet, there is no consensus regarding the definition of OHT evaluated by HBPM (*32*). Previous studies have used different definitions to describe the prevalence of OHT. One found an OHT prevalence of 10% (defined as a supine diastolic blood pressure [DBP] below 90 mmHg and standing DBP above 90 mmHg) in hypertensive patients (*6*). Another report (using a definition of an SBP rise of 20 mmHg upon standing) found the prevalence to be 8.7% in elderly subjects (*8*). In a third study of elderly hypertensive patients, this value was 20% (defined as an SBP rise of 10 mmHg during the tilt test) (*33*) and in normotensive diabetic patients (*34*), it was 12.8% (defined as an increase in DBP from <90 to ≥ 90 mmHg and/or an increase in SBP from <140 to ≥ 140 mmHg after standing from the supine position). In the present study, we defined OHT as inclusion in the top decile group, which had an orthostatic BP change of >7.8 mmHg as evaluated by HBPM, which might be a high-risk group for hypertensive subjects in terms of BNP levels and the UAR. When we defined OHT using 10 mmHg as the threshold of orthostatic BP change, the prevalence of OHT was 6.9% and OHT was also significantly associated with an increased UAR.

Another interesting finding in this study is that OHYPO is not associated with UAR or BNP. Previously, OHYPO has been shown to contribute to target organ damage and coronary heart disease (*1–6*). This discrepancy might be explained by the differences between the study's subjects. We recruited patients whose morning SBP with HBPM was ≥ 135 mmHg, because it has been reported that morning hypertension is a risk factor for cardiovascular events (*35*). Sympathetic nerve hyperactivity is among the mechanisms that lead to morning hypertension and we previously reported that subjects with OHT have high morning BP levels (*9*). Therefore, we speculate that the subjects in this group might have had increased sympathetic nerve activity, which could have contributed to the greater extent of target organ damage.

Clinical Implications

This study is the first to show that OHT evaluated by HBPM is associated with the UAR and with BNP levels, independently of the sitting home BP level. About 10% of hypertensive patients may have OHT, which is considered to be a high-risk factor for an increased UAR and elevated BNP and is also associated cardiovascular events. Thus, the evaluation of OHT may be important for detecting high-risk individuals and also for potentially establishing a new therapeutic target for evaluating specific treatments that suppress the orthostatic BP increase and prevent target organ damage in hypertensive patients.

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