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ORIGINAL ARTICLE

Impact of depression on masked hypertension and variability in home blood pressure in treated hypertensive patients

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This study was conducted to determine the effects of depression and/or insomnia on masked hypertension (MHT) compared with other types of HT and on variability in home-measured blood pressure (HBP) and clinic BP (CBP). Three hundred and twenty-eight hypertensives (132 women) aged 68 ± 10 years were classified into four BP types: controlled HT (CHT), white-coat HT, MHT and sustained HT (SHT), based on CBP (140/90 mm Hg) and morning HBP (135/85 mm Hg) measurements. A score of ⩾16 on the Center for Epidemiologic Studies Depression Scale (CES-D) was defined as depression. The mean values and s.d. of BP were calculated from measurements taken during the 14 consecutive days just before the CES-D evaluation. Compared with the CHT group, the risk of depression was 2.77-fold higher in the SHT group and even higher in the MHT group (7.02-fold). The association between depression and MHT was augmented in the presence of insomnia and was somewhat stronger in women. A HBP variability index defined as s.d./mean BPs in both morning and night time was significantly higher in MHT than in the other BP types, whereas that of CBP was not. Both morning and night-time HBP variability were significantly higher in depressive patients than in non-depressives. These suggest that depression is associated with MHT and that increases both morning and night-time HBP variability but not CBP variability. Physicians should be mindful of mental stresses such as depression in their hypertensive patients when forming strategies to control BP over the diurnal cycle.
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INTRODUCTION

Home-measured blood pressure (HBP) is an ideal method for diagnosis and treatment of hypertension (HT) in daily practice and also a stronger predictor of cardiovascular disease (CVD) risk than clinic BP (CBP).[1–6] HT can be classified into four types based on home and clinic BP measurements: controlled HT (CHT), white coat HT (WHT), masked HT (MHT) and sustained HT (SHT).[7] Numerous previous studies have shown that the risk of cardiovascular events in patients with MHT is significantly higher than that in patients with CHT or WHT, and is either similar to or moderately higher than that in patients with SHT.[8–12] Meanwhile, abnormal variations of BP during the diurnal cycle, from day by day, and between clinic visits are also associated with an increased risk of cardiovascular events.[13–16] Further, a relationship between diurnal variations in BP and prognosis has been established.[7]

Previous studies reported that mental stresses such as anxiety and depression influence the diurnal variations of BP[7] and are associated with both new onset and younger onset of HT.[17–20] The risk of adverse CVD outcomes in patients with coronary artery disease is higher in those who suffer from anxiety,[21] and mortality and the risk of myocardial infarction in hypertensive patients are higher in those who suffer from depression.[22] In an earlier study by our group on 120 treated hypertensive patients assessed by 24-h ambulatory BP monitoring (ABPM), the presence of anxiety disorders evaluated by the Hospital Anxiety and Depression Scale (HADS) was significantly associated with nocturnal HT, early morning HT and increased BP variation in both night time and early morning, irrespective of the presence of a morning BP surge.[23] Similarly, a recent report using HADS and ABPM in Turkish hypertensive patients identified anxiety and depression as independent predictors of non-dipper HT.[24] Meanwhile, Kario *et al.*[25] showed gender differences in the associations between depression and anxiety scales assessed by the Brief Symptom Inventory and BP variations evaluated by ABPM in healthy working men and women.

The findings from these studies underline the importance of evaluating psychological background factors and mental stress when selecting treatments for HT and the prevention of CVDs. Even so, no reported studies to date have evaluated how depression relates to

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variations in clinical and non-clinical BP and/or MHT in treated hypertensive patients, or whether any gender differences are to be found in these relationships. This study was conducted to determine the effects of depression and/or insomnia on MHT compared with other types of HT and the effects of depression on visit-to-visit variability of CBP and day-by-day variability of HBP in patients with treated HT.

METHODS

Subjects

Three hundred and twenty-eight consecutive outpatients with essential HT (196 men and 132 women, mean age 68 ± 10 years) who visited the Showa University Hospital during the 2-year period from November 2011 to October 2013 were enrolled. Patients were excluded from the study if they had histories of any conditions known to affect circadian BP patterns, namely, lethal ventricular arrhythmia, atrial fibrillation, pacemaker implantation, symptomatic valvular heart disease and left ventricular dysfunction characterized by an ejection fraction of <45% evaluated by echocardiography; primary kidney disease and renal dysfunction characterized by an estimated creatinine clearance of $<45\,ml\,min^{-1}$ using the Cockcroft–Gault formula;[26] uncontrolled diabetes mellitus characterized by a glycated hemoglobin (Hb) A1c (National Glycohemoglobin Standardization Program (NGSP)) level ⩾8.0%, previously diagnosed sleep apnea syndrome, stroke or other neuromuscular disorders.[27–30] Patients who changed doses and/or the classes of oral antihypertensive drugs within the past year were also excluded. This study was designed as a cross-sectional study and was approved by the ethics committee of the Showa University Hospital. Written informed consent was obtained from all of the patients before participation. The investigation conformed to the principles of the Declaration of Helsinki.

Baseline examination

The blood level of HbA1c (NGSP) and serum levels of creatinine, triglyceride and high-density lipoprotein cholesterol were measured using standard laboratory procedures. Low-density lipoprotein cholesterol levels were measured with a direct homogenous assay (Sekisui Medical, Tokyo, Japan). Diabetes mellitus was defined as a fasting serum glucose value $>126\,mg\,dl^{-1}$, HbA1c values >6.5% and/or current use of medication for diabetes.[31] Patients who were currently using lipid-lowering medications and/or met the following criteria of the Japan Atherosclerosis Society for fasting serum lipid levels were considered to have dyslipidemia: low-density lipoprotein cholesterol ⩾140 $mg\,dl^{-1}$, high-density lipoprotein cholesterol $<40\,mg\,dl^{-1}$ or triglyceride $\geqslant 150\,mg\,dl^{-1}$. [32] Body mass index was calculated as weight (kg) divided by height (m) squared. The coronary artery disease was defined as myocardial infarction and/or angina pectoris based on coronary arteriograms, and a prior history of coronary revascularization. Patients who reported a smoking habit of at least one cigarette per day were classified as current smokers. Patients who reported daily or occasional drinking were classified as alcohol consumers.

Definition of depression and insomnia

We evaluated the presence of depression by having the patients fill out the Japanese version of Center for Epidemiologic Studies Depression Scale (CES-D).[33] The CES-D comprises 20 items, each rated on a 4-point (0–3) scale, allowing for a maximum score of 60. The patients were instructed to answer the questions as immediate responses, and completed the CES-D questionnaire in the normally allotted time of 3 to 5 min. Patients who were taking antidepressants and/or whose score was ⩾16 were defined as having significant depression.[34] Patients were defined as insomniacs if they responded 'over 3 days per week' to the question 'My sleep was restless', or answered 'yes' to the question 'Do you usually take sleeping pills or minor tranquillizer as a sleep aid?'[33]

BP and heart rate measurements

CBP measurements were taken at each visit by a physician using a mercury sphygmomanometer with the patient in the sitting position after a 1–2 min rest. Systolic BP was measured at Korotkoff sound 1 and diastolic BP was measured at Korotkoff sound 5. Pulse was measured with the radial artery for 1 min. The mean values and s.d. of the CBP and pulse rates were calculated based on measurement taken in 8–12 visits within 1 year from the completion of the questionnaire. The visit-to-visit variability of CBP was defined as the percentage difference in the coefficient of variation (CV, defined as s.d./mean × 100).

The patients measured their BPs and pulse rates at home in the morning within 1 h after waking up (after urination, before breakfast and medication) and at night time just before sleeping. The measurements were taken according to the guidelines of the Japanese Society of Hypertension after 1–2 min of sitting at rest using a commercially available oscillometric digitalized device with an upper arm cuff and digital memory.[4] We instructed the patients to measure the BP only once at each occasion and this value was analyzed. The mean values and s.d. of BPs and pulse rates were calculated using measurements taken for the 14 consecutive days just before the date of the CES-D. Day-by-day variability of HBP was defined as the percentage difference in the CV.

HT management was classified into four groups based on the cut-off levels of morning HBP (135/85 mm Hg) and CBP (140/90 mm Hg): CHT (HBP<135-/85 mm Hg and CBP<140/90 mm Hg); WHT (HBP<135/85 mm Hg and CBP⩾140/90 mm Hg); MHT (HBP⩾135/85 mm Hg and CBP<140/90 mm-Hg) and SHT (HBP⩾135/85 mm Hg and CBP⩾140/90 mm Hg).[7] Summations of antihypertensive drugs were calculated according to the doses and classes of drugs taken. The numbers given for the drugs are expressed as relative ratios to the standard doses and summed to a total. The combination of 12 mg of candesartan (1.5), 12.5 mg of hydrochrolothiazide (0.5) and 10 mg of amlodipine (2), for example, was calculated as 4. The number of patients who received ⩾3 different antihypertensive drugs is shown.

Statistical analysis

All statistical analyses were performed using the JMP version 10 statistical software package (SAS institute, Tokyo, Japan). Categorical variables are presented as numbers of patients (percentages). Continuous variables are expressed as mean ± s.d. or median and interquartile ranges, according to their distributions. The difference in frequency data was determined by the X^2-test for categorical variables. The association of depression or insomnia among four groups of BP control and that of MHT among four groups based on depression and/or insomnia were calculated as odds ratios (ORs) and 95% confidence intervals using age and gender adjusted logistic regression analysis. Morning and night-time HBP variability index, and CBP variability index were compared for continuous variables using the analysis of variance with Tukey's honest significant difference test to identify differences among the four groups. Statistical significance was set at $P<0.05$.

RESULTS

The clinical characteristics of the four groups are shown in Table 1. There were significantly more men than women in the SHT group and fewer men than women in the WHT and MHT groups. The MHT and SHT patients scored significantly higher on the CES-D than the CHT and WHT patients. The prevalence of coronary artery disease was significantly lower in SHT than in CHT or MHT. The distributions of antihypertensive drugs used were similar, but the summation of antihypertensive drugs was significantly higher in the MHT patients compared with the CHT patients, and still higher in the SHT patients. The number of patients who received ⩾3 different antihypertensive drugs was significantly higher in SHT than in CHT or WHT.

Depression and management of HT

Figure 1 shows the prevalence of the depression among the four groups. Thirty-two of 196 men (16.3%) and 38 of 132 women (28.8%) were depressive. Half of the patients with MHT and about 30% of SHT patients were depressive, and the prevalence of depression in MHT and SHT was significantly higher compared with those in CHT and WHT. Furthermore, depression was significantly more in MHT patients and MHT women than those in SHT counterparts. Age and gender-adjusted ORs for having depression were 7.02, 8.08 and

Table 1 Comparison of clinical characteristics among the four groups of hypertension control

	CHT (n = *178*)	*WHT* (n = *44*)	*MHT* (n = *60*)	*SHT* (n = *46*)
CES-D score	8.2 ± 6.1	9.3 ± 6.1	14.0 ± 7.0*,#	11.5 ± 5.8*
Age, years	68.0 ± 10.5	68.4 ± 9.0	68.5 ± 11.1	66.6 ± 9.3
Female, *n* (%)	64 (36)	25 (57)*	31 (52)*	12 (26)#,§
Height, cm	161.8 ± 9.3	159.3 ± 10.0	159.1 ± 8.9	161.1 ± 7.1
Weight, kg	62.9 ± 12.3	63.1 ± 12.8	61.4 ± 11.8	64.9 ± 11.9
Body mass index, kg m^{-2}	23.9 ± 3.7	24.7 ± 3.7	24.1 ± 3.4	25.0 ± 4.1
Clinic measurements				
Systolic BP, mm Hg	125.4 ± 9.3	147.7 ± 9.1*	129.6 ± 6.5#	148.7 ± 12.0*,§
Diastolic BP, mm Hg	74.8 ± 7.8	84.9 ± 6.8*	76.3 ± 10.6#	84.3 ± 11.4*,§
Heart rate, beats per min	71.8 ± 9.4	71.1 ± 8.9	70.8 ± 8.9	70.0 ± 9.8
Home measurements (morning)				
Systolic BP, mm Hg	123.6 ± 8.0	124.9 ± 6.6	144.6 ± 7.4*,#	146.4 ± 9.3*,#
Diastolic BP, mm Hg	73.5 ± 9.2	72.7 ± 9.0	83.3 ± 9.8*,#	83.5 ± 10.7*,#
Heart rate, beats per min	66.4 ± 9.6	65.7 ± 8.0	67.8 ± 8.1	67.2 ± 10.2
Home measurements (night time)				
Systolic BP, mm Hg	119.1 ± 10.2	122.1 ± 12.2	132.8 ± 13.8*,#	137.5 ± 12.5*,#
Diastolic BP, mm Hg	69.2 ± 9.3	71.1 ± 11.0	77.0 ± 11.1*,#	80.0 ± 17.6*,#
Heart rate, beats per min	68.5 ± 9.8	67.7 ± 8.2	68.7 ± 8.7	68.3 ± 10.3
Diabetes mellitus, *n* (%)	29 (16)	5 (11)	12 (17)	12 (22)
Dyslipidemia, *n* (%)	108 (61)	24 (55)	39 (65)	20 (44)
Coronary artery disease, *n* (%)	66 (37)	8 (18)*	23 (38)#	8 (17)*,§
Laboratory data				
24 h Ccr, ml min^{-1}	78.2 ± 25.6	82.2 ± 27.5	80.1 ± 31.6	81.3 ± 29.4
Triglyceride, mg dl^{-1}	126.0 ± 73.2	120.1 ± 69.2	133.0 ± 86.9	122.9 ± 67.3
HDL-cholesterol, mg dl^{-1}	54.6 ± 15.7	56.1 ± 15.4	55.1 ± 18.3	54.4 ± 13.5
LDL-cholesterol, mg dl^{-1}	99.9 ± 27.1	111.1 ± 31.4	104.1 ± 27.3	113.8 ± 35.3*
HbA1c (NGSP), %	6.3 ± 0.9	6.0 ± 0.7	6.1 ± 1.0	6.0 ± 0.6
Medications, n *(%)*				
ACEI and/or ARB	139 (78)	35 (79)	49 (82)	44 (96)
Calcium channel blocker	91 (51)	25 (57)	34 (57)	33 (72)
β-blocker	50 (28)	6 (14)	17 (28)	16 (35)
Diuretics	20 (11)	6 (14)	13 (22)	8 (17)
Statins	101 (57)	23 (52)	35 (58)	18 (39)
Sleeping pills	20 (11)	3 (7)	12 (20)*,#	2 (4)§
Minor tranquilizer	9 (5)	4 (9)	11 (18)*,#	3 (7)§
Antidepressants	1 (0.6)	0 (0)	2 (3)	2 (4)
Patients with ⩾3 different antihypertensive drugs	29 (16.3)	6 (13.6)	17 (28.8)	18 (39.1)*,#
Summations of oral antihypertensive drugs	1.8 ± 1.2	1.8 ± 1.1	2.3 ± 2.5*	2.6 ± 1.1*,§
Alcohol cosumption, *n* (%)	87 (49)	19 (43)	22 (37)	25 (54)
Current smokers, *n* (%)	73 (41)	22 (50)	19 (32)	22 (48)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; Ccr, creatinine clearance; CES-D, Center for Epidemiologic Studies depression scale; NGSP, National Glycohemoglobin Standardization Program.
*$P<0.05$ *vs.* CHT, #$P<0.05$ *vs.* WHT, §$P<0.05$ *vs.* MHT.
Data given as mean ± s.d. or *n* (%).

5.95 in MHT patients, MHT men and MHT women, compared with CHT counterparts, respectively. On the other hand, risk of having depression was similar among CHT, WHT and SHT in women.

Insomnia and management of HT

Figure 2 shows the prevalence of insomnia among the four groups. About 40% of the MHT patients had insomnia, and the prevalence of insomnia was significantly higher in MHT compared with CHT. In addition, the prevalence of insomnia was significantly higher in MHT women compared with that in WHT and SHT women. Age-adjusted ORs for having insomnia in men and women with MHT had a 3.36 and 3.55, respectively, compared with CHT counterparts. The prevalence of insomnia was comparable among the CHT, WHT and SHT patients.

Association with Depression, insomnia and MHT

Figure 3 shows the prevalence of MHT among the four groups based on the presence or absence of depression and insomnia. Sixty-one percent of depressive patients had insomnia while 61% of patients with insomnia had depression. Depressive patients had significantly

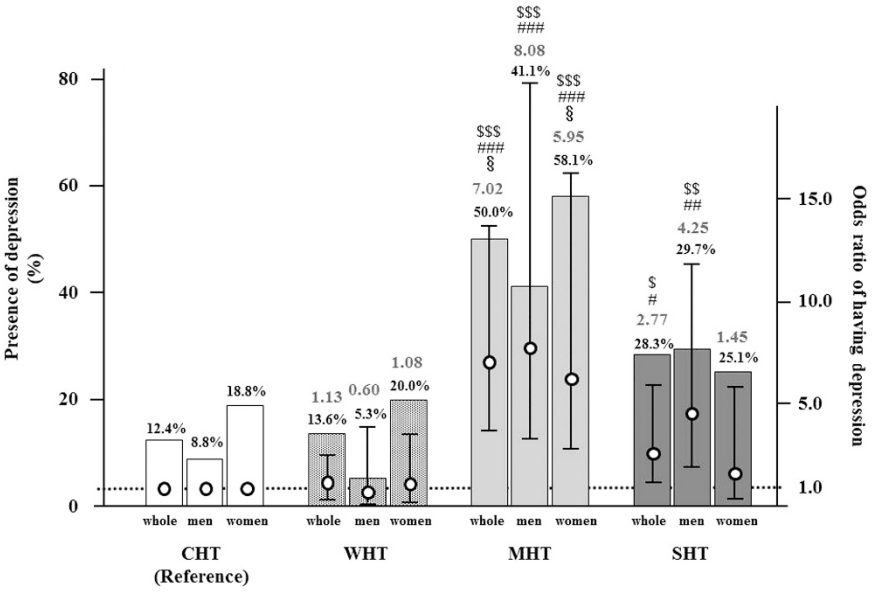

Figure 1 Comparison of the presence of depression among the four blood-pressure-control groups. Twenty-two (10 men), 6 (1 man), 29 (11 men) and 13 (10 men) patients in the CHT, WHT, MHT and SHT groups suffered from depression, respectively. Odds ratio of having depression in WHT, MHT and SHT patients compared with that in CHT patients were adjusted for age and gender. $^{\$}P<0.01$, $^{\$\$}P<0.005$, $^{\$\$\$}P<0.0001$ *vs.* CHT, $^{\#}P<0.01$, $^{\#\#}P<0.005$, $^{\#\#\#}P<0.0001$ *vs.* WHT, $^{\S}P<0.05$ *vs.* SHT. CHT, controlled hypertension; MHT, masked hypertension; SHT, sustained hypertension; WHT, white-coat hypertension. A full color version of this figure is available at *Hypertension Research* online.

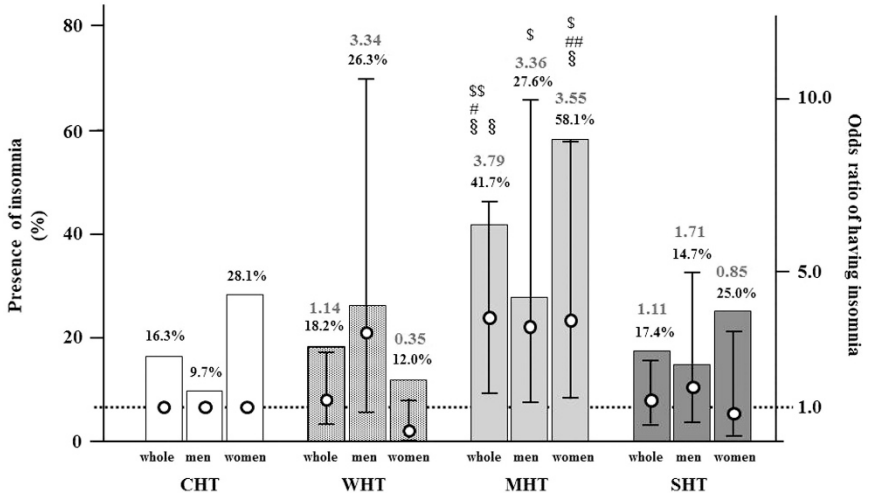

Figure 2 Comparison of the presence of insomnia among the four blood-pressure-control groups Twenty-nine (11 men), 8 (5 men), 25 (8 men), and 8 (5 men) patients in the CHT, WHT, MHT and SHT groups had insomnia, respectively. Odds ratio of having insomnia in WHT, MHT and SHT patients compared with that in CHT patients were adjusted for age and gender. $^{\$}P<0.05$, $^{\$\$}P<0.001$, *vs.* CHT, $^{\#}P<0.05$, $^{\#\#}P<0.005$ *vs.* WHT, $^{\S}P<0.05$, $^{\S\S}P<0.01$ *vs.* SHT. CHT, controlled hypertension; MHT, masked hypertension; SHT, sustained hypertension; WHT, white-coat hypertension. A full color version of this figure is available at *Hypertension Research* online.

higher risk of MHT irrespective of the presence of insomnia. Besides, depressive patients with insomnia had markedly higher risk of MHT compared with those without depression, and age and gender-adjusted ORs were 8.38 (95% confidence interval, 3.36–22.76).

Effects of depression and gender on the prevalence of the four BP types and BP variability

Table 2 shows the prevalence of the four BP types and the CVs of HBP and CBP among the four groups based on gender and the presence of depression. The prevalence of CHT, WHT, MHT and SHT among these four groups significantly differed ($P<0.001$). The prevalence of MHT was significantly higher in depressive men and women (34.4% and 47.4%, respectively) than in their non-depressive counterparts (10.4% and 13.8%, respectively). The CVs of both morning and night-time HBP were significantly higher in depressive patients than in their non-depressive counterparts. There were no significant differences in the CVs of CBP among the four groups. Figure 4 shows the CVs of the day-by-day home systolic BP measured in the morning and night time and the CVs of the visit-to-visit systolic CBP in all four groups. The CVs of the morning systolic HBP were significantly higher in MHT

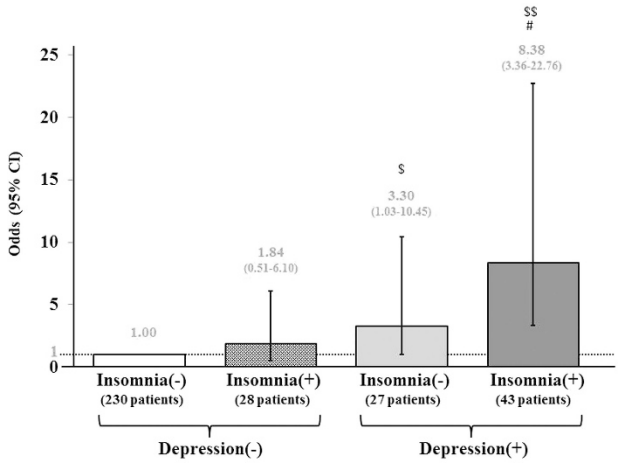

Figure 3 Comparison of incidence of MHT among the four groups based on the presence of depression and insomnia. Bars represent age and gender-adjusted odds ratios and of 95% confidence intervals having MHT compared with patients without depression and insomnia as control. The number of patients in non-depression/non-insomnia, non-depression/insomnia, depression/non-insomnia and depression/insomnia groups are 230, 28, 27 and 43, respectively. $^{\$}P<0.05$, $^{\$\$}P<0.0001$ *vs.* non-depression/non-insomnia, $^{\#}P<0.05$ *vs.* non-depression/insomnia group. MHT, masked hypertension. A full color version of this figure is available at *Hypertension Research* online.

Table 2 Comparison of blood pressure control and variability index of home and clinic systolic blood pressure

	Men		*Women*	
	Non-depressive (n = *164*)	*Depressive* (n = *32*)	*Non-depressive* (n = *94*)	*Depressive* (n = *38*)
CHT, *n* (%)	105 (64.0)	10 (31.3)	52 (55.3)	12 (31.6)
WHT, *n* (%)	18 (11.0)	1 (3.1)	20 (21.3)	5 (13.2)
MHT, *n* (%)	17 (10.4)	11 (34.4)	13 (13.8)	18 (47.4)
SHT, *n* (%)	24 (14.6)	10 (31.3)	9 (9.6)	3 (7.9)
BP variability index (%)				
HBP (morning)	5.4 ± 2.0	6.9 ± 2.6*,#	6.0 ± 2.1	6.8 ± 2.5*,#
HBP (night time)	6.4 ± 2.4	7.6 ± 3.1#	6.1 ± 2.6	7.0 ± 2.5#
CBP	7.0 ± 2.7	8.2 ± 3.1	7.0 ± 2.5	7.4 ± 2.3

Abbreviations: BP, Blood pressure; CBP, clinic blood pressure; CHT, controlled hypertension; HBP, home-measured blood pressure; MHT, masked hypertension; SHT, sustained hypertension; WHT, white coat hypertension.
*$P<0.05$ *vs.* non-depressive men, #$P<0.05$ *vs.* non-depressive women.
Data given as mean ± s.d. or *n* (%).

than in CHT, WHT or SHT, and the CVs of night-time HBP were significantly higher in MHT than in CHT or WHT. The CVs of the CBP were similar among the four groups.

DISCUSSION

To the best of our knowledge, this study is the first study to show that treated patients with MHT had significantly higher risks of depression and insomnia compared with patients with CHT or WHT, as well as patients with SHT. On the other hand, the presence of depression and/or insomnia in patients with HT was strongly associated with MHT, and the combination markedly increased a risk for MHT. Further, depressive patients and patients with MHT showed significantly higher day-by-day variability in morning and night-time HBP than patients with CHT, WHT or SHT, whereas no such increase was found in the visit-to-visit variability of CBP.

A meta-analysis of nine prospective cohort studies reported that depression was an important factor to consider when forming strategies to prevent or treat HT.[35] However, several studies showed no association between depression and HT,[36] and even inverse association between depression and systolic BP[37,38] or diastolic BP.[39–41] In addition, it remains controversial how depression and other psychometric factors affect BP control. Konstantopoulou *et al.*[42] reported that MHT diagnosed by ABPM was more strongly associated with mood behavior in the hypomania–euthymia range and a lower score for type-A personality, which suggest lower depressive, compared with WHT and SHT. Terracciano *et al.*[43] have showed that reduced conscientiousness was significantly associated with an increased risk of MHT among treated hypertensives. On the other hand, the Finn-Home study reported that MHT was associated with hypochondria and depression.[10] Jokisalo *et al.*[44] found that a hopeless attitude, frustration with treatment and perceived tension with BP measurement are associated with poor BP control in hypertensive patients. Di Matteo *et al.*[45] showed that depressed patients are likely to have poor BP control because they lose interest in adhering to their therapeutic regimen. In a recent report from Rubio Guerra *et al.*[46] on 40 hypertensive patients who complied well with antihypertensive therapy, depressive status appeared to be a risk factor of poorly controlled BP determined by self-measurement. A recent case-control study from Pakistan showed a significant association between uncontrolled HT and depression evaluated by HADS.[47] Symonides *et al.*[48] have recently proposed that the suppression of negative emotions adversely affect BP control evaluated by ABPM in treated hypertensive patients. All of these reports support our results. As regards to insomnia and BP control, there were few studies to show how sleep disturbance affects BP control. Loredo *et al.*[49] reported that deeper and less-fragmented sleep was associated with more BP dipping in normal adults. On the other hand, Paciência *et al.*[50] reported that longer sleep duration might increase likelihood of high BP in 13-year-old women but not in men. Matthews *et al.*[51] reported that elevated night time BP evaluated by ABPM was associated with sleep disturbance (difficulty in falling asleep, fragmented sleep) evaluated by actigraphy. Although the biological mechanisms involved in the relationship between depression or insomnia and MHT are still poorly understood, the present study clearly shows that depression or insomnia is associated with MHT, and the coexistence of depression and insomnia was strongly associated with MHT.

Our present findings specifically showed a significantly pronounced relationship between depression or insomnia and MHT in women. The lower rate of SHT in women partly explains this association and weakens the evidence of a gender effect. Gender difference in the BP response to mental stress may partly explain the association.[52,53] Our group speculates that a visit to a physician may bring more mental relief to depressive women than to depressive men, thereby reducing the clinic BP of the former. Future studies are required to examine the precise mechanism of gender difference in BP response to mental stress.

Regarding the BP variability, the CVs of the morning and night-time HBP were significantly higher in the MHT group than in the other three groups. The day-by-day variability of HBP is reported to have prognostic significance for CVD.[7] Few studies, however, have assessed how depression affects the variability of HBP or CBP in hypertensive patients. The Finn-Home study showed that day-by-day

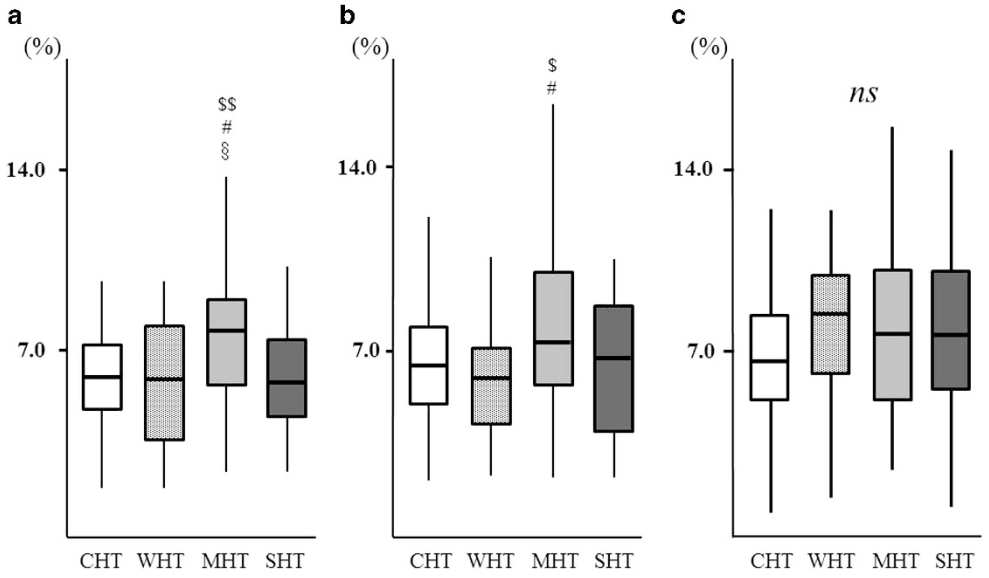

Figure 4 Comparison of the variability index of home and clinic systolic blood pressure. The figure shows the CVs of the day-by-day systolic blood pressure (SBP) variability of morning home BP (HBP) (**a**) and night-time HBP (**b**) and the visit-to-visit SBP variability of clinic BP (**c**) among the four groups. The CVs of the morning systolic HBP were 5.7 (1.5–10.1), 5.6 (1.1–10.2), 7.1 (2.0–13.0) and 5.3 (1.9–10.5) in CHT, WHT, MHT, and SHT, respectively. The CVs of the night-time systolic HBP were 6.0 (2.0–11.5), 5.7 (2.5–10.0), 7.1 (2.2–15.2) and 6.4 (2.6–10.3) in CHT, WHT, MHT and SHT, respectively. The boxes indicate the 25th and 75th percentiles and the lines indicate the 5th and 95th percentiles. $^{\$}P<0.05$, $^{\$\$}P<0.001$ *vs.* CHT, $^{\#}P<0.001$ *vs.* WHT, $^{\S}P<0.005$ *vs.* SHT. BP, Blood pressure; CBP, clinic blood pressure; CHT, controlled hypertension; CV, coefficient of variation; HBP, home-measured blood pressure; MHT, masked hypertension; NS, not significant; SHT, sustained hypertension; WHT, white coat hypertension.

variability in morning and evening HBP was significantly higher in participants with persistent insomnia than in those without insomnia.[54] This finding may support the present result.

In a recent report on 825 middle-aged hypertensive Japanese males, persistent depression evaluated by CES-D was found to be a significant risk factor for the development of arteriosclerosis determined by changes of brachial-ankle pulse wave velocity.[55] It is likely that the presence of depression contributes to an increase of HBP and variability of HBP, which further increases CVD risk in patients with HT. It has been well established that MHT determined by HBP is associated with a poor prognosis of CVDs.[1] The present study provides important findings for the management of HT in clinical practice.

Study limitations

This study has several limitations. First, we investigated a relatively small number of patients. Second, the antihypertensive drugs and doses used to treat the MHT and SHT may have been inappropriate for some of the patients. Third, we neglected to consider several conditions associated with resistant HT, namely, dietary salt consumption, alcohol consumption, physical activity, adherence to antihypertensive drugs and sleep-disordered breathing such as sleep apnea in our MHT and SHT patients. Fourth, we were unable to evaluate sympathetic nervous activity because the ambulatory status of our hypertensive outpatients made it impossible to measure a direct index of sympathetic nervous activity. Fifth, we did not consider seasonal BP variations. Sixth, we excluded hypertensive patients with advanced organic damage. Finally, we could not evaluate how the treatment for depression affected BP management in our hypertensive patients. Future studies to evaluate these questions with larger numbers of patients will be needed.

CONCLUSION

Depression is associated with MHT, and the association between depression and MHT is likely to be stronger in women. Moreover, a depressive state increases both morning and night-time HBP variability in patients with essential hypertension. Physicians should be mindful of mental stresses such as depression in their hypertensive patients when forming strategies to prevent CVD and control BP over the diurnal cycle.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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