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Reproducibility of Morning Blood Pressure Surge and Its Relation to Blood Pressure Reactivity

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This study examined the stability of the morning blood pressure surge (MBPS) and its relation to blood pressure (BP) reactivity in untreated hypertensives. Thirty-six participants completed a stress task at baseline. Ambulatory BP monitoring was carried out three times on a weekday. The MBPS demonstrated small reproducibility and large coefficient of variation. The MBPS correlated with nighttime BP ($p = 0.001$) but not morning BP or BP reactivity. Dippers had greater MBPS than did nondippers ($p < 0.05$). The MBPS provides distinct information that is different from the BP response to mental stress.

Keywords blood pressure reactivity, coefficient of variation, morning blood pressure surge, nocturnal dipping, reproducibility

Excessive morning blood pressure surge (MBPS) has been demonstrated to be a predictor of cerebrovascular events (1,2) and cardiovascular target organ damage (3). Previous studies have explored factors that could be involved in the control of the increase in blood pressure (BP) in the morning. Circadian variation of the autonomic nervous activity can affect the morning BP. In a study of medicated hypertensives, older age, alcohol drinking, and β-blocker use were determinants of the morning-evening BP difference (4), a surrogate measure of the MBPS. These data suggest that increased sympathetic nervous system (SNS) activity is a key physiological mechanism of exaggerated MBPS. In a study of general population, age and central obesity were found to be significant determinants of the MBPS (5). Because increased activity of the SNS was found to be associated with increased central obesity (6), it is possible that an endogenous surge of the SNS activity is involved in the control of the MBPS.

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Abrupt changes in physical activity have been demonstrated to be associated with the MBPS in hypertensives (7). In one study comprised of a heterogeneous group in terms of age range and BP, the magnitude of the MBPS was found to be dependent on levels of physical activity (8). Furthermore, it has been demonstrated that the increase in BP and heart rate (HR) in the morning seems to be controlled by direct sympathetic neural input to the heart and vasculature in response to activity and posture changes rather than by the intrinsic fluctuations of plasma catecholamines (9). Hence, exaggerated physical activity-induced SNS activation after arising from bed may be thus far the most plausible etiology for the excessive MBPS.

Exaggerated BP responses to mental stress reflect activation of the SNS, and/or vagal withdrawal and provide another index of the sympathetic activation. It has been demonstrated that larger mental stress-induced BP reactivity is associated with silent cerebrovascular disease in healthy older adults (10). Hostility has been found to be associated with exaggerated MBPS in hypertensives (11). In addition, it has been demonstrated that BP reactivity was negatively correlated to diurnal BP variation (i.e., sleep/awake BP ratio; 12). Thus, it is likely that excessive MBPS merely reflects exaggerated BP reactivity to stress.

To date, the question on whether MBPS is associated with BP reactivity to mental stress remains to be determined. Moreover, the reproducibility of the MBPS as a predictor remains uninvestigated. We therefore conducted this study to examine the reproducibility of the MBPS over 5 to 12 weeks and the possible correlates of the MBPS, in particular its association with BP reactivity to stress, in a group of untreated, newly diagnosed hypertensives.

Methods

Participants

Participants were all newly diagnosed with hypertension and had never been treated with anti-hypertensive medications. Participants were recruited via public BP screening or referred by a cardiologist. Those passing the initial screen were invited to undergo a detailed eligibility evaluation. Exclusion criteria were history of cardiovascular disease, diabetes mellitus, renal disease, hepatic disease, neurological disease, psychiatric disorders, or medications affecting central nervous system. Thirty-six community-dwelling hypertensive individuals, aged 20 to 55, participated in this study. All participants provided written informed consent.

Study Procedure

All participants were tested at baseline for anthropometric measurements, BP, and HR. Age in years, sex, educational level, marital status, parental history of hypertension, smoking habit, and regular exercise habit (> 2 hours/week) were also collected at baseline. They were also subject to a laboratory-induced stress protocol. Ambulatory BP monitoring (ABPM) was carried out three times on a weekday (weeks 1, 5, and 12).

Office Blood Pressure and Heart Rate Measurements

BP and HR were recorded by an automatic noninvasive cuff-oscillometric recorder (Model 90217, SpaceLabs™ Inc., Redmond, Washington, USA). This monitor measured

BP through the detection of oscillations transmitted from the brachial artery to the cuff. The SpaceLabs ™ monitor is equipped with four different size adult cuffs. A SpaceLabs ™ model 9029 Data Interface Unit was used for report generation. The SpaceLabs monitor was programmed to show readings of BP and HR. Multiple resting measurements 2 minutes apart were taken 5 minutes after participants were seated. The mean of the two readings that agreed within 5 mmHg was defined as the office BP and HR.

Anthropometric Measurements

Anthropometric measurements examined in this study included body height in centimeter, weight in kilogram, and body mass index (BMI, kg/m^2).

Laboratory Stress Testing

Preceded by a 30 min adaptation period, a laboratory stress session was employed to induce BP reactivity. Participants were asked to complete the Stroop Color and Word Test (SCWT). The SCWT is composed of a color-name reading task, a color-naming task, and an interference task. The effect of the SCWT in inducing sympathetic responses has been previously reported (13). The stress session consisted of a 4 min baseline and a task period while beat-to-beat BP and HR were recorded using Finometer (TNO Biomedical Instrumentation, Amsterdam, Netherlands). The Finometer device permits the reconstruction of brachial pressure from non-invasive finger arterial pressure measurements by applying a generalized waveform filter.

Ambulatory Blood Pressing Monitoring

ABPM was recorded using the SpaceLab monitor (Model 90217, SpaceLabs™ Inc., Redmond, Washington, USA). In cooperation with the participant, ABPM was scheduled on a day that represents the participant's typical day of the week, during which he/she was to keep a regular sleep and wake pattern. The ABPM was performed on week 1 and repeated on weeks 5 and 12. Participants were discouraged to wear the ABP monitor during off-work/school days or days with special life events (e.g., job interview, examination). No shift workers were included in this study. Competitive sports and strenuous leisure activities were prohibited during ABPM. The monitor was programmed to take BP measurements every 30 min during the day and evening (6 a.m. to 10 p.m., i.e., awake time) and every 60 min during the night (10 p.m. to 6 a.m., i.e., sleep time) for a 24-hour period. Participants were given a diary and were instructed to record the time they go to sleep and the time they wake up.

Calculation

The day–night SBP difference, or nocturnal SBP reduction, was calculated as the difference between the mean daytime (awake) pressure and the mean nighttime (sleep) pressure, using the individual boundaries between periods of sleep and wake time as indicated by each participant's diary. MBPS was calculated as the average morning SBP minus the lowest nighttime SBP. The lowest nighttime SBP is defined as the lowest reading that occurred during the sleep period. The morning SBP is defined as the average of SBP during the first two hours after waking (four readings). Beat-to-beat BP and HR were recorded throughout the laboratory stress testing. SBP reactivity was calculated by subtracting the mean SBP during the baseline period from the mean SBP during the task period.

Subgrouping

Participants whose mean nighttime SBP is at least 10% lower than the mean daytime SBP were defined as *dippers* whereas in *nondippers* no decline in mean nighttime SBP was noted or the decline did not exceed 10%. *Extreme dippers* were defined as those with a ≥20% nocturnal reduction in SBP. The dipper status was assessed using the first ABPM.

Data Analysis

Data were analyzed using the SPSS 11.5 for Window software (SPSS Inc., Chicago, Illinois, USA). Pearson correlation coefficients were calculated to determine the reproducibility of the MBPS measurement. Within-subject variation was determined by examining the difference in MBPS between weeks for each participant using the paired t-test. Due to large between-subject variations (i.e., large standard deviations of the mean) in the MBPS, natural log-transformed MBPS values were used in the paired t-test. The coefficient of variation (CV) of MBPS was also calculated. The agreements among three repeated measurements were assessed using Bland-Altman analysis (14). The Bland-Altman plot was performed using the MedCalc software (MedCalc Software, Mariakerke, Belgium). Relationships of the magnitude of the MPBS to age, BMI, office BP and HR, and ambulatory BP and HR measurements were examined using the Pearson correlational analysis. A *t*-test was used to compare the magnitude of the MBPS between men and women. Comparisons of the ABPM measures and the MBPS between the three dipper groups were performed with a type III test using the General Linear Model, with the dipping status as a fixed factor and age as a covariate. A p value < 0.05 was considered significant.

Results

A total of 36 individuals (23 men and 13 women), aged 20 to 55 (mean=43.1, S.D.=10.9) years, participated in the study. The bio-demographic and lifestyle data of the study participants at baseline were presented in Table 1. The correlation coefficients of the MBPS measurements between weeks 1 and 5, weeks 5 and 12, and weeks 1 and 12 were 0.41, 0.38, 0.57, respectively (all $p < 0.05$). As can be seen in Table 2, the difference in natural log-transformed MBPS between weeks assessed by paired t-test was not statistically significant. However, the within-subject CV was large (28.9%). Similarly, the nocturnal SBP dipping demonstrated a large within-subject CV (44.3%). The agreement between the MBPS measurements taken on different weeks was assessed by the Bland-Altman analysis (see Figure 1). The results from the Bland-Altman analysis demonstrated that the limits of agreement between any one pair of the MPBS measurements (i.e., week 1 versus 5, week 1 versus 12, and week 5 versus 12) were large and not clinically acceptable.

The within-subject variation in the ambulatory 24-hour average SBP and DBP, daytime and nighttime HR measurements, were also examined using the paired t-test and Pearson correlation coefficient (see Table 3). The CVs of these ambulatory measurements were also calculated. As can be seen on Table 3, the within-subject CVs of the 24-hour average SBP and DBP, daytime and nighttime HR were small (3.9%, 4.6%, 6.2%, and 5.3%, respectively). The nighttime SBP was inversely correlated to MBPS (r=-0.52, p=0.001, see Figure 2). However, the relationship between morning SBP level and MBPS did not reach statistical significance(r=0.18, p=0.29). The larger the standard deviations of the 24-hour BP and HR and the larger the nocturnal SBP dipping, the greater the MBPS was (r=0.70, $p < 0.001$; r=0.35, p=0.04; r=0.55, $p < 0.001$, respectively). The magnitude of

Table 1
Baseline bio-demographic and lifestyle data of the study participants

Variable	Value
Age (years)	43.1 ± 10.9
Sex (%)	
Women	36.1
Men	63.9
Marital status (%)	
Yes	76.3
No	23.7
Educational level (%)	
Less than high school	5.3
High school	23.7
College and above	71
BMI (kg/m^2)	26.2 ± 3.4
Office SBP (mmHg)	145.4 ± 8.0
Office DBP (mmHg)	94.4 ± 8.3
Office HR (bpm)	76.4 ± 8.3
Parental history of hypertension (%)	
Yes	71.1
No	29.9
Smoker (%)	
Yes	13.2
No	86.8
Regular exercise (%)	
Yes	60.5
No	39.5

Abbreviations: BMI=body mass index; DBP=diastolic blood pressure; HR=heart rate; SBP=systolic blood pressure.

the MBPS was not correlated to age, BMI, office SBP and HR, 24-hour SBP and HR, or daytime SBP and HR (p=0.51, 0.53, 0.36, 0.48, 0.38, 0.12, 0.95, and 0.08, respectively). The difference in the magnitude of the MPBS between men and women was not statistically different (p=0.11).

SBP reactivity to stress was not significantly correlated with the MBPS (see Figure 3). Similarly, SBP reactivity was not significantly correlated with nocturnal reduction in SBP (r=0.09, p=0.60). A comparison of the bio-demographic and lifestyle characteristics of the three dipper groups (i.e., nondippers, dippers, and extreme dippers) revealed that age, sex, BMI, martial status, education, parental history of hypertension, smoking and exercise habits were not significantly different among groups (p=0.98, 0.25, 0.73, 0.96, 0.32, 0.60, 0.15, and 0.67, respectively). Similarly, office SBP and DBP, 24-hour SBP and DBP, and daytime SBP and DBP, as well as nighttime DBP, were not significant different among groups (see Table 4). As expected nighttime SBP was significantly different among the three dipper groups ($p < 0.001$). Moreover, the level of the MBPS was significantly different among the three dipper groups (p=0.001). Pair-wise contrasts revealed

Table 2
Within-subject variation in the morning blood pressure surge and nocturnal blood pressure dipping

	MBPS Mean ± SD (mmHg)	Dipping Mean ± SD (mmHg)
Week 1 (W1)	29.1 ± 12.5	17.4 ± 10.4
Week 5 (W5)	25.2 ± 12.7	15.6 ± 8.3
Week 12 (W12)	28.7 ± 9.6	16.2 ± 8.2
Paired t-test*		
W1–W5	0.26 ± 0.94 (NS)	0.16 ± 0.79 (NS)
W5–W12	−0.28 ± 0.94 (NS)	−0.04 ± 0.70 (NS)
W1–W12	0.02 ± 0.37 (NS)	0.10 ± 0.85 (NS)
Correlation (*r*)		
W1–W5	0.41†	0.41†
W5–W12	0.38†	0.32†
W1–W12	0.57†	0.43†
CV	28.9%	44.3%

Abbreviations: MBPS=morning blood pressure surge; W1–W5=measurement difference (or correlation) between weeks 1 and 5 paired by subject; W5–W12= measurement difference (or correlation) between weeks 5 and 12 paired by subject; W1–W12=measurement difference (or correlation) between weeks 1 and 12 paired by subject; NS=not significant. CV is the coefficient of variation=(S.D./μ)×100%, where S.D. is the standard deviation of mean weeks 1, 5, and 12, and μ is the average of weeks 1, 5, and 12.

*log-transformed values were used in the paired-*t* test.

†$p < 0.05$.

that the MBPS was significantly larger in dippers as compared with nondippers ($p=0.004$). The MBPS was also significantly larger in the extreme dippers than in the nondippers ($p < 0.001$). However, the difference in the MBPS between dippers and extreme dippers were not statistically significant ($p=0.13$).

Discussion

In light of recent interests on the phenomena of excessive MBPS as a predictor of cerebrovascular events and cardiovascular target organ damage, it is important for researchers to have an understanding of the stability of the MBPS over time. The results from the study demonstrated the first evidence that the MBPS derived from ABPM measurements taken from a group of nonmedicated mild hypertensives is not a stable measurement over time. The observed wide limits of agreement between each pair of the MBPS measurements, the small test-retest correlation coefficients, and the large within-subject CV suggest that the MBPS might not be a stable trait in never-treated mild hypertensive individuals.

The lack of reproducibility of the MBPS could possibly be due to the effects of weather (15) and day of the week (16) on 24-hour BP profile. In addition, salt loading has been demonstrated to exacerbate the MBPS (17). A persistent (i.e., reproducible) nocturnal non-dipping pattern, but not a variable (i.e., non-reproducible) one, is associated with

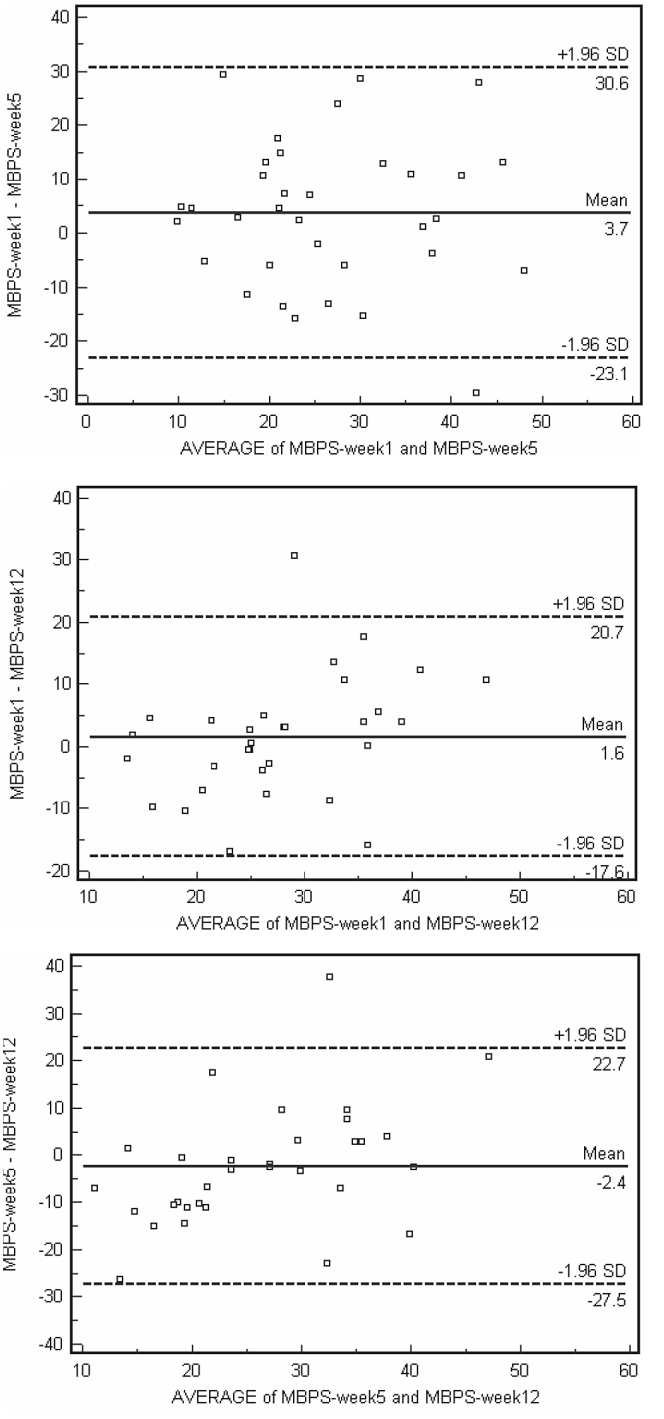

Figure 1. Bland-Altman plots of the agreement between three repeated measurements. The y-axis shows the magnitude of the differences, and the x-axis displays the mean morning blood pressure surge (MBPS) values. The upper to lowest panel shows agreement between weeks 1 and 5, weeks 1 and 12, and weeks 5 and 12, respectively.

Table 3
Within-subject variation in the ambulatory 24-hour average blood pressure and daytime and nighttime heart rate measurements

	24-hour blood pressure (mmHg)		Heart rate (bpm)	
	Systolic Mean ± SD	Diastolic Mean ± SD	Daytime Mean ± SD	Nighttime Mean ± SD
Week 1 (W1)	133.7 ± 9 .76	87.6 ± 9.0	80.2 ± 9.6	63.6 ± 6.7
Week 5 (W5)	131.9 ± 11.6	85.7 ± 10.0	79.6 ± 7.7	63.5 ± 6.9
Week 12 (W12)	133.0 ± 9.784	86.36 ± 9.8	79.9 ± 9.1	64.5 ± 8.2
Paired t-test				
W1-W5	NS	NS	NS	NS
W5-W12	NS	NS	NS	NS
W1-W12	NS	NS	NS	NS
Correlation (*r*)				
W1-W5	0.67*	0.79*	0.55*	0.75*
W5-W12	0.49*	0.66*	0.54*	0.66*
W1-W12	0.44*	0.66*	0.74*	0.72*
CV	3.9%	4.6%	6.2%	5.3%

Abbreviations: W1–W5=measurement difference (or correlation) between weeks 1 and 5 paired by subject; W5–W12=measurement difference (or correlation) between weeks 5 and 12 paired by subject; W1–W12=measurement difference (or correlation) between weeks 1 and 12 paired by subject; NS=not significant.
*$p < 0.05$.

greater cardiovascular target organ damage (18), suggesting that ambulatory BP profile should be diagnosed with multiple ABPM measurements instead of a single ABPM. It is also interesting to learn that a so-called α-adrenergic MBPS was calculated as the baseline MBPS minus the MBPS during α_1-blocker therapy in a previous study (19). Findings from the present study call the reproducibility of the MBPS into question and caution a possible misattribution of a reduction in the MBPS over time to α-antagonist-induced MBPS reduction. It must be acknowledged, however, that participants included in this study were newly diagnosed and were at relatively younger ages, whereas participants included in previous studies were established hypertensive elderly (1,19). In addition, the magnitude of the MBPS was smaller than that reported by the previous studies (1,19). The mild hypertensives in the present study might not have developed the characteristic BP variation that is capable of predicting cardiovascular events. In addition, the middle-aged population might demonstrate a circadian BP profile that is very different from their older counterparts. Therefore, the lesser degree of target organ damage and younger age might account for the lack of stability of the MBPS observed in the present study.

One may also argue that the small reproducibility of MBPS observed in this study might be due partially to the different physical activity levels between the days of ABPM. However, a careful inspection of the ambulatory HR data revealed that the coefficient of variation across three days of measurements was negligible. Similarly, 24-hour ambulatory BP data also had a small coefficient of variation across three days of measurements. Hence, the difference in the level of physical activity could not explain the observed small reproducibility of MPBS.

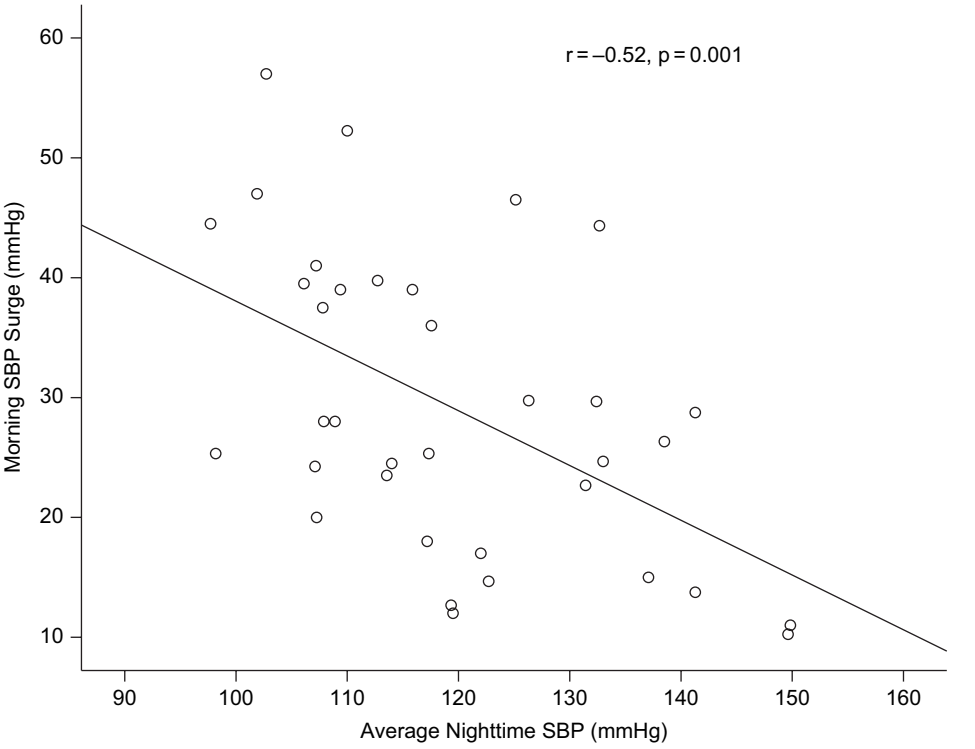

Figure 2. The relation between average nighttime SBP and MBPS. SBP = systolic blood pressure.

It has been demonstrated that there is a circadian rhythm in basal vascular tone due at least partly to increased α-sympathetic vasoconstrictor activity during the morning (20). Previous data of a suppression of the MBPS by α-adrenergic blockade further support this notion (19). On the other hand, data in the present study showed that morning BP level and BP reactivity to stress are not significant correlates of the MBPS seem to against the notion that physical activity-induced increased α-sympathetic vasoconstrictor activity during the morning underlines the MBPS. The magnitude of the MBPS was largely determined by the nighttime reduction in BP rather than the morning elevation in BP. Participants' dipper status was also related to the magnitude of the MBPS even after adjusting for the possible effect of age. These data lead to the speculation that the MBPS and nocturnal dipping are in fact two concepts of the same origin. One can argue that in this particular hypertensive sample, the activation of the SNS after arising from sleep and during the waking hours played a minor role in the morning surge, leading to small MBPS. That is, there might not been true surgers in this middle-aged hypertensive sample.

Exaggerated stress-induced BP reactivity has been suggested to be a potential risk factor for cerebrovascular disease (10). The possibility of target organ damage modulating the association between cardiovascular reactivity and diurnal BP variation has been reported (12). Incidences of cardiovascular events display a diurnal pattern and tend to be higher in the morning than at other times of day. BP also displays a circadian pattern. In the present study, we tested whether an excessive morning surge in BP merely reflects

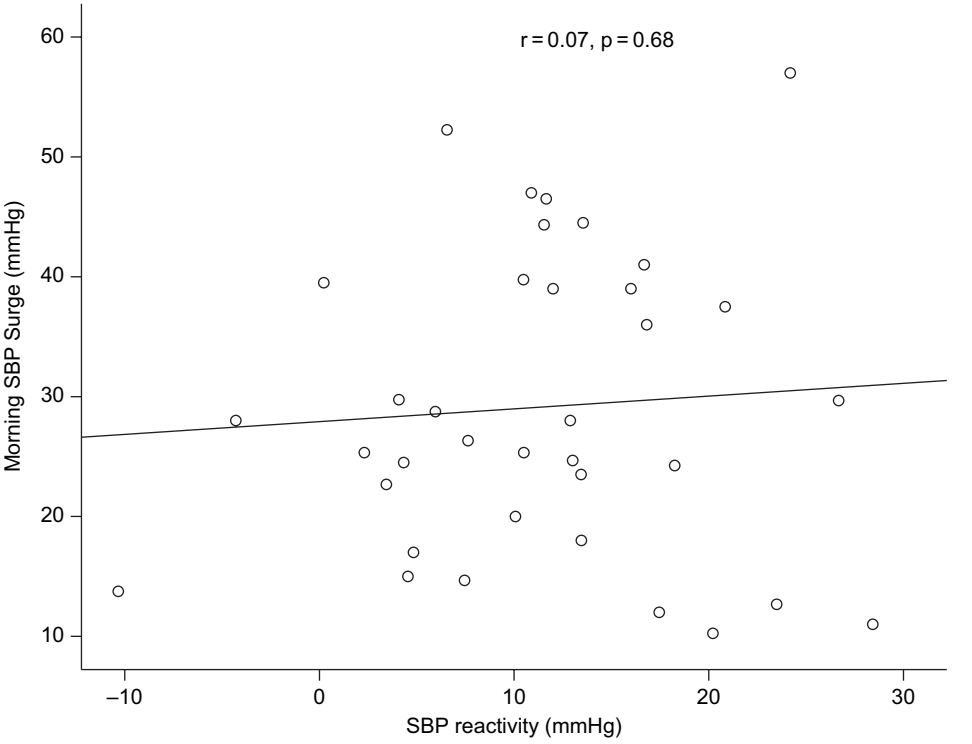

Figure 3. The relation between SBP reactivity and MBPS. SBP = systolic blood pressure.

exaggerated BP reactivity to mental stress. Although results should be interpreted with caution because of the small sample size, we found that the magnitude of the MBPS was not related to the level of BP reactivity to mental stress. Then, an exaggerated pattern of stress reactivity cannot explain the link between cardiovascular events and MBPS in the middle-aged mild hypertensives without organ damage.

In this study, we found that the nocturnal BP dipping had small reproducibility and large CV. This finding may be interesting because it coincides with results from a previous study in which the dipping pattern (i.e., non-dipping or dipping status) of non-diabetic hypertensive patients were not stable over a four-week period (21). Together with the finding of a non-reproducible MBPS, the finding of a non-reproducible nocturnal BP dipping cautions the use of derived ABPM parameters in clinical research.

This study is limited by its small sample size and wide range of age group. Small reproducibility and large CV of MBPS might be in part due to the small sample size. Therefore, readers should exercise cautions when interpreting the results. In summary, the MBPS is not a stable measure over time. The MBPS provides distinct information that is very different from the BP response to mental stress.

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Table 4
Comparisons of blood pressure parameters among groups with different dipper status

	Nondipper (n=13) Mean (SD)	Dipper (n=16) Mean (SD)	Extreme dipper (n=7) Mean (SD)	ANCOVA* F	ANCOVA* *p*
SBP					
Office	148.1 (8.4)	143.0 (8.6)	145.1 (3.5)	1.60	0.21
24 hour	136.9 (9.6)	131.8 (10.8)	131.5 (6.4)	1.22	0.31
Daytime	138.6 (9.3)	136.4 (11.4)	138.5 (6.7)	0.23	0.80
Nighttime	131.4 (11.4)	116.1 (11.5)]†	106.1 (5.8)‡	15.13	< 0.001
DBP					
Office	93.4 (10.0)	94.5 (6.6)	96.3 (9.0)	0.36	0.70
24 hour	87.0 (10.2)	88.3 (8.3)	87.4 (9.0)	0.11	0.89
Daytime	88.7 (9.3)	91.7 (8.6)	92.3 (9.3)	0.61	0.55
Nighttime	81.6 (13.6)	76.2 (9.6)	69.7 (7.6)	3.0	0.07
MBPS	20.1 (9.6)	32.0 (10.9)†	39.3 (10.8)‡	8.93	0.001

Abbreviations: ANCOVA=analysis of covariance; DBP=diastolic blood pressure; MBPS=morning blood pressure surge; SBP=systolic blood pressure.

*Comparisons of the measurements between groups with a type III test using the General Linear Model, with the dipper status as a fixed factor and age as a covariate.

†Dippers versus nondippers, $p < 0.05$.

‡Extreme dippers versus nondippers, $p < 0.05$.

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