ORIGINAL ARTICLE

Morning Blood Pressure Surge as a Predictor of Outcome in Patients with Essential Hypertension

Mohamed Y. Abdel-Khalik, Shereen A. Mahrous[2], Alsayed A. Shanab, Abdullah M. Alshehri[1], Mustafa H. Rashed, Ayman M. Azoz

Department of Cardiac Technology, College of Applied Medical Sciences, [1]Department of Cardiology, College of Medicine, University of Dammam, [2]Department of Family Medicine, Primary Health Care Center in Dammam, Ministry of Health, Saudi Arabia

Correspondence: Dr. Mohamed Y. Abdel-Khalik, King Abdulaziz Street, Alzohoor Neighborhood, P.O. Box 1982, Dammam 31441, Saudi Arabia. E-mail: mykhalil@uod.edu.sa

ABSTRACT

Objective: To determine the usefulness of monitoring morning blood pressure surge (MBPS) to predict cardiovascular events in patients with essential hypertension.

Materials and Methods: A total of 81 patients (43 males and 38 females) with a mean age of 55.9 ± 9.8 years with essential hypertension were included in the study. Twenty-four hour ambulatory blood pressure (BP) monitoring was carried out to record MBPS. All patients were followed up for 36 months for cardiovascular events.

Results: Mean MBPS was 26.23 ± 10.17 mmHg. Nineteen patients (23%) who experienced a cardiovascular event during the follow-up period had higher MBPS than patients who did not experience a cardiovascular event ($P < 0.0001$). MBPS was positively correlated with interventricular septum thickness ($r = +0.38$ and $P = 0.000$), left atrial size ($r = +0.39$ and $P = 0.000$), 24-h mean systolic BP ($r = +0.36$ and $P = 0.001$) and total cholesterol level ($r = +0.23$ and $P = 0.003$). MBPS was negatively correlated with high-density lipoprotein-cholesterol ($r = -0.37$ and $P = 0.001$).

Conclusion: MBPS can be used as a biomarker for a cardiovascular disease event in hypertensive patients.

Key words: Cardiovascular events, essential hypertension, morning blood pressure surge

ملخص البحث:

تهدف هذه الدراسة إلى التعرف على مدى فائدة رصد وقياس ضغط الدم الصباحي كمؤشر للتنبؤ بمضاعفات القلب والشرايين لدى المرضى المصابين بارتفاع ضغط الدم. شملت الدراسة 81 مريضاً بارتفاع ضغط الدم تم رصد ضغط الدم لديهم خلال 24 ساعة لتسجيل القراءات وتمت متابعتهم لمدة 36 شهراً لملاحظة أي مضاعفات بالقلب. اتضح من الدراسة أن 23% من مرضى الضغط الذين عانوا مضاعفات كانت قراءات رصد وقياس ضغط الدم الصباحي أعلى لديهم من أولئك المرضى الذين لم يعانوا من مضاعفات قلبية. ينصح الباحثون إلى أهمية رصد وقياس ضغط الدم الصباحي كمؤشر للمضاعفات القلبية لدى المرضى المصابين بارتفاع ضغط الدم.

INTRODUCTION

Systemic blood pressure (BP) is characterized by daily fluctuation in the form of peaks and troughs or a circadian rhythm.[1] Morning BP surge (MBPS) is defined as the sleep-trough surge, calculated by subtracting the morning BP (mean of four readings over 2 h just after waking up) from the lowest nocturnal BP (mean of three readings around the lowest nighttime).[2]

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Several factors are responsible for MBPS, including increased physical activity, sympathetic nervous system and renin-angiotensin-aldosterone system activities.[3] In hypertensive patients, there is a disruption in the production of nitric oxide with more than the normal increase that occurs in normotensives in the early morning hours. This results in a further vasoconstrictor effect, which in turn causes an abrupt increase in BP.[4]

MBPS is an independent risk factor for cardiovascular events. It is associated with cerebral events and target organ damage.[5] Patients with high MBPS have an increase in left ventricular (LV) mass, prolonged corrected QT interval and longer QT dispersion.[6,7] In a previous study, for every 10 mmHg increase in morning systolic BP (SBP), the risk of stroke increased by 22%.[8] MBPS is encountered more frequently in females and in the elderly.[9] Type-II diabetic patients with high MBPS have a higher incidence of adverse events compared to those who do not experience high MBPS.[10]

MATERIALS AND METHODS

A cross-sectional study was conducted with a total number of 81 patients (43 males and 38 females) who were recruited from patients with chronic disease attending the outpatient clinic from June 2012 to June 2015.

Inclusion criteria included patients who had essential hypertension. Patients who had secondary hypertension, decompensated heart failure, uncontrolled diabetes mellitus, refractory angina, acute coronary syndrome, infants, children, pregnant women and patients included in other research projects were excluded from the study cohort. Ethical approval from the Institutional Review Board was obtained. All patients signed a written informed consent form prior to participating in the study.

The medical records of the patients included in the study were evaluated. In addition, these patients had a thorough clinical examination, including calculation of body mass index (BMI) as (weight [kg]/height [m]^2). Moreover, these patients had a fundus examination on 6-month intervals until the end of the follow-up period. Baseline resting echocardiography using Vivid S5 machine equipped with 2.5 MHz transducer was performed in the lateral decubitus position with measurement of the LV dimensions and assessment of LV ejection fraction. The LV diastolic function was assessed by mitral valve flow waves (E/A ratio) and tissue Doppler imaging from the mitral valve annulus and pulmonary venous flow pattern. In addition, evaluation of the LV regional wall motion abnormalities, measurement of left atrium size, assessment of right side dimensions and estimation of pulmonary artery systolic pressure were performed.

Baseline blood tests

A venous blood sample was drawn from each patient (10-h fasting) to obtain a complete blood picture, renal and liver functions, fasting blood sugar, 2-h postprandial blood sugar, glycosylated hemoglobin (HbA1C), total serum cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, serum uric acid and microalbuminuria. Microalbuminuria was measured using the albumin/creatinine ratio (ACR) in one single morning spot urine sample. Microalbuminuria was defined as an ACR ≥3.0 mgmmol^{-1}.[11] BP measurements were obtained using WXB-50 model sphygmomanometer.

Ambulatory blood pressure monitoring

A 24-h ambulatory blood pressure monitoring (ABPM) was measured by a TONOPORT V device. The readings were recorded by protocol P3 by which BP was recorded at 30-min intervals in the daytime and at 60-min at nighttime. The respective daytime and nighttime hours were defined using certain time intervals which ranged from 6 am to 10 pm and 10 pm to 6 am. Maximal inflation pressure during the daytime phase was 250 mmHg and during the night phase was 220 mmHg. Cardio-Soft version 6.73 software (GE Healthcare) was utilized to assess the recordings. The mean values of daytime, nighttime and 24-h SBP and diastolic BP (DBP) were calculated for each patient on the basis of hourly averages of ambulatory BP recordings. MBPS is calculated from subtracting the morning SBP (mean SBP for 2 h just after waking up) from the lowest nocturnal SBP during sleep. Participants who showed a nocturnal fall of ≥10% in SBP were considered dippers.[5]

All patients were followed up for 36 months. Every 3 months, the patients were assessed by telephone contact. Every 6 months, the patients were assessed at the outpatient clinic, during which clinical, echocardiographic and laboratory evaluations were performed. Patients were followed up to detect any evidence of adverse clinical events such as:

- Cardiac events: Acute coronary syndrome, pulmonary edema and cardiac arrhythmias
- Neurological events: Hypertensive encephalopathy, transient ischemic attacks, cerebral infarction and cerebral hemorrhage
- Renal impairment
- Death

Data were statistically analyzed using IBM SPSS (Statistical Package for Social Science) program version 20 for Windows (SPSS Inc., Chicago, IL, USA). All analyses were considered statistically significant at 95% confidence interval and $P < 0.05$. Descriptive analysis for data in the form of mean, frequency and percentage was performed. Chi-square test was done for qualitative variable analysis and *t*-test (independent *t*-test) was done to compare the mean values of males with females. Pearson's correlation test was done to detect a relationship between MBPS and all measured variables. ROC curve (receiver operating characteristic curve) was done to detect the cut level of any tested variable, where at this level, there are the best sensitivity and specificity cutoff values of the variables for the presence of the disease.

RESULTS

The study population included 81 patients with chronic disease attending the outpatient clinic from June 2012 to June 2015. The study cohort consisted of 43 males (53%) and 38 females (47%) with a mean age 55.9 ± 9.8 (range 36–73 years old). Table 1 shows the patients' characteristics, including their pharmacological therapy.

All patients were followed up for 36 months. The patients were classified into two groups according to their clinical outcome during the follow-up period. The first group included patients who had not experienced a cardiovascular event and the second group included 19 patients (23%) who had experienced a cardiovascular event during the follow-up period [Table 2].

Table 3 shows the differences in the patients' baseline characteristics, including risk profile and laboratory and echocardiographic data between the two groups. Patients who had experienced a cardiovascular event during the follow-up period were generally in the older age group and had an abnormal lipid profile and higher blood glucose level. However, there were no differences between the two groups regarding BMI, duration of hypertension and smoking.

Patients who experienced a cardiovascular event during this period also had a higher serum TC, LDL-cholesterol, lower HDL-cholesterol and higher HbA1c level. In addition, they had higher ventricular septum thickness ($P = 0.005$) and higher left atrial size ($P = 0.010$) compared with patients who had not experienced a cardiovascular event. Furthermore, there was a significant difference between the two groups according to the grade of diastolic dysfunction [Figure 1].

Patients who experienced a cardiovascular event had higher 24-h mean SBP, higher MBPS ($P > 0.0001$) and nondipper pattern ($P = 0.0171$). However, there were no differences between the two groups regarding office BP readings ($P > 0.152$) and 24-h mean DBP ($P > 0.195$) [Table 4]. Table 5 shows the correlation of MBPS with clinical, laboratory and ambulatory BP parameters.

Table 1: Patient's characteristics

Variables	Total patients (*n* = 81)
Age (mean ± SD)	55.9 ± 9.8
BMI	28.8 ± 4.6
Risk profile (%)	
Diabetes mellitus	19 (24)
Dyslipidemia	24 (30)
Smoking	20 (25)
Pharmacological therapy (%)	
Diuretics	26 (32)
B-blockers	34 (42)
Calcium channel blockers	19 (24)
ACIEs	26 (32)
ARBs	19 (24)
Office SBP (mmHg)	153.3 ± 11.19
Office DBP (mmHg)	92.4 ± 7.7
24-h mean SBP (mmHg)	141.4 ± 11.8
24-h mean DBP (mmHg)	88.6 ± 16.5
Daytime mean SBP (mmHg)	145.1 ± 12.9
Daytime mean DBP (mmHg)	88.3 ± 7.6
Nighttime mean SBP (mmHg)	132.7 ± 10.1
Nighttime mean DBP (mmHg)	81.4 ± 6.0
MBPS (mmHg)	26.23 ± 10.17

SBP – Systolic blood pressure; DBP – Diastolic blood pressure; MBPS – Morning blood pressure surge; B-blockers – Beta-blockers; ACIEs – Angiotensin converting enzyme inhibitors; ARBs – Angiotensin receptors blockers; BMI – Body mass index; SD – Standard deviation

Table 2: Clinical outcome of the 81 patients within 36 months

36-month clinical outcome	State (yes/no)	*n* (%)
Neurological complications	No	75 (92.5)
	Yes	6 (7.5)
Acute coronary syndrome	No	75 (92.5)
	Yes	6 (7.5)
Hypertensive encephalopathy	No	77 (95)
	Yes	4 (5)
Flash pulmonary edema	No	80 (98.75)
	Yes	1 (1.25)
Microalbuminuria	No	79 (97.5)
	Yes	2 (2.5)

Table 3: Differences in baseline characteristics, risk profile and laboratory data in the studied patients

Variables	Group 1	Group 2	*P*
Age	49.7 ± 8.3	62.5 ± 7.6	0.000
BMI	28.6 ± 4.6	29.9 ± 3.1	0.214
HTN duration (years)	5.3 ± 2.9	6.8 ± 3.8	0.060
DM, *n* (%)	12 (63)	7 (37)	0.049
Dyslipidemia, *n* (%)	13 (54.2)	11 (45.8)	0.010
Total cholesterol (mg/dl)	203.4 ± 39.1	242.1 ± 33.7	0.043
HDL-C (mg/dl)	42.9 ± 7.1	33.9 ± 6.2	0.032
LDL-C (mg/dl)	127.3 ± 25.2	161.6 ± 17.3	0.013
TG (mg/dl)	160.3 ± 64.2	245.9 ± 61.7	0.045
Creatinine (mg/dl)	0.90 ± 0.19	0.92 ± 0.25	0.677
Uric acid (mg/dl)	5.56 ± 1.23	5.68 ± 0.91	0.678
HbA1c (%)	5.73 ± 1.15	6.7 ± 0.79	0.024
IVS thickness (cm)	0.81 ± 0.75	1.18 ± 0.43	0.005
LA size (cm)	3.3 ± 0.07	4.2 ± 0.05	0.010

Group 1 – Patients who didn't develop cardiovascular events. Group 2 – Patients who developed cardiovascular events. BMI – Body mass index; HTN – Hypertension; DM – diabetes mellitus; IVS – Interventricular septum; LA – Left atrium; HDL-C – High-density lipoprotein cholesterol; LDL-C – Low-density lipoprotein cholesterol; TG – Triglycerides; HbA1c – Glycosylated hemoglobin

Table 4: Differences in baseline characteristics according to blood pressure findings

Blood pressure variables (mmHg)	Group 1	Group 2	*P*
Office SBP	150.5 ± 10.2	155.24 ± 10.19	0.152
Office DBP	91.6 ± 7.07	94.4 ± 9.18	0.169
24-h mean SBP	137.9 ± 9.5	151.3 ± 12.0	0.0001
24-h mean DBP	88.5 ± 18.8	88.9 ± 6.6	0.195
Daytime mean SBP	141.5 ± 10.7	155.2 ± 13.5	0.0001
Daytime mean DBP	87.2 ± 7.4	91.7 ± 7.3	0.019
Nighttime mean SBP	129.7 ± 8.5	141.2 ± 9.6	0.0001
Nighttime mean DBP	80.5 ± 6.5	83.9 ± 3.3	0.021
MBPS	21.19 ± 6.5	36.37 ± 5.33	0.0001

Group 1 – Patients who did not develop cardiovascular events. Group 2 – Patients who developed cardiovascular events. SBP – Systolic blood pressure; DBP – Diastolic blood pressure; MBPS – Morning blood pressure surge

There were weak positive correlations between MBPS and TC level ($r = +0.23$ and $P = 0.003$); interventricular septum (IVS) thickness ($r = +0.38$ and $P = 0.000$); left atrial size ($r = +0.39$ and $P = 0.000$) and 24-h means SBP ($r = +0.36$ and $P = 0.001$). There was a weak negative correlation between MBPS and HDL-cholesterol ($r = -0.37$ and $P = 0.001$). There were non-significant positive correlations between MBPS and age ($r = +0.19$); BMI ($r = +0.24$); HbA1c ($r = +0.24$) and LDL-cholesterol ($r = +0.26$).

Independent *t*-tests showed that there were no significant differences in the mean BP surge between males and females ($t = 0.41$, $P = 0.68$); diabetic and non-diabetic patients ($t = 1.19$, $P = 0.24$) as well as smokers and nonsmokers ($t = 0.18$, $P = 0.86$).

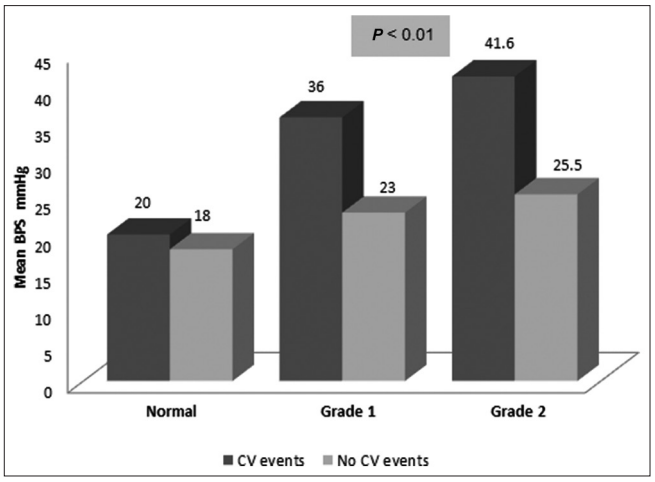

Figure 1: State of left ventricular diastolic function and mean BPS in the studied patients. BPS – Blood pressure surge; Grade 1 – Grade 1 left ventricular diastolic dysfunction; Grade 2 – Grade 2 left ventricular diastolic dysfunction

DISCUSSION

Hypertension is considered a powerful risk factor for cardiovascular diseases, including ischemic heart disease, cerebrovascular disease, LV dysfunction, renal impairment and peripheral vascular diseases.[2]

BP has a diurnal variation; it decreases during sleep and surges in the morning.[12] MBPS is defined as the variance between the systolic blood pressure (SBP) 2 hours after waking and the mean SBP during sleep.[13]

ABPM is required to examine the sleep and awake differences. Measurement of BP in the early morning and soon after arising provides much of the clinically relevant data that can be utilized to detect patients who are at risk.[14]

Regarding MBPS and age, our findings showed an insignificant positive correlation between MBPS and age and the association lost significance in adjusted analysis ($P = 0.07$). These findings are in agreement with Neutel *et al.*, who found that higher MBPS is associated with increased age.[1] However, in the multivariate analysis, age was not significantly associated with MBPS. This may be due to other confounding factors such as the variability of BP in elderly patients. Elsurer and Afsar and Sun *et al.* reported that there was significant positive correlation between MBPS and age in hypertensive patients and this association remained significant even after adjusted analysis.[15,16]

Table 5: Correlations between morning blood pressure surge and other variables

Variables	*R*	*P*
Age	+0.19	0.07
BMI	+0.24	0.03
HTN duration	+0.07	0.56
Total cholesterol (mg/dl)	+0.32	0.003
HDL-C (mg/dl)	−0.37	0.001
LDL-C (mg/dl)	+0.26	0.02
TG (mg/dl)	+0.17	0.06
Creatinine (mg/dl)	−0.09	0.4
uric acid (mg/dl)	−0.3	0.79
HbA1c (%)	+0.24	0.03
IVS thickness	+0.38	0.000
LA size	+0.39	0.000
24-h mean SBP (mmHg)	+0.36	0.001
24-h mean DBP (mmHg)	+0.04	0.75
Daytime mean SBP (mmHg)	−0.33	0.002
Daytime mean DBP (mmHg)	+0.031	0.79
Nighttime mean SBP (mmHg)	+0.29	0.01
Nighttime mean DBP (mmHg)	−0.004	0.97

BMI – Body mass index; HTN – Hypertension; HDL-C – High-density lipoprotein cholesterol; LDL-C – Low-density lipoprotein cholesterol; TG – Triglycerides; HbA1c – Glycosylated hemoglobin; IVSD – Interventricular septal diameter; LA – Left atrium; SBP – Systolic blood pressure; DBP – Diastolic blood pressure

The present study shows that there was no significant positive correlation between MBPS and BMI ($P = 0.03$). A previous study by Lee *et al.* reported a statistically insignificant association between MBPS and BMI but the patients in that study were not receiving antihypertensive therapy while in our study, all the patients were under treatment.[17] Furthermore, in another study by Neutel *et al.*, MBPS was not affected by BMI in hypertensive patients.[1]

Regarding the association between MBPS and lipid profile, our findings showed that MBPS was positively correlated with TC level, LDL-cholesterol and negative correlation with HDL-cholesterol. However, there was no significant association between MBPS and serum TGs. Similar results were reported by Turak *et al*.[18] Moreover, Elsurer and Afsar reported that there was a significant positive correlation between MBPS and TC, LDL-cholesterol and TGs and a negative correlation with HDL-cholesterol, but this association was not statistically significant.[15]

The present study showed that MBPS can be used to predict cardiovascular risk in hypertensive patients. Patients who developed cardiovascular events had higher BP surge ($P < 0.0001$).

In this study, we found that an MBPS cutoff value of 41 mmHg had a sensitivity of 100% and specificity of 80% to predict cerebrovascular events ($P > 0.001$) and a cutoff value of 33 mmHg had a sensitivity of 91% and specificity of 79% to predict acute coronary syndrome ($P > 0.001$). These findings are in agreement with Gosse *et al*., who showed that there was a significant association between rising BP surge and cardiovascular events independent of age and 24-h BP level ($P < 0.009$).[19] However, in our study, there was a positive correlation between 24-h mean SBP and MBPS ($r = 0.36$).

Similar results were obtained by Amici *et al*., who studied the association between MBPS and cardiovascular risk in elderly hypertensive patients with a mean age of 66 years and followed them for 5 years.[20] He showed that those with a sleep-trough surge >34 mmHg had a higher cardiovascular risk than those with a surge <34 mmHg ($P < 0.001$). However, in our study, it was independent of age. Our results are in agreement with Li *et al*., who concluded the following, "MS above the 90th percentile significantly and independently predicted cardiovascular outcome and might contribute to risk stratification by ABPM.[21]

This study showed that there was positive correlation between IVS thickness and LA size and both 24-h mean SBP and MBPS ($P = 0.000$). In addition, it showed that patients who developed cardiovascular events had a greater IVS thickness ($P = 0.005$) and larger left atrial size ($P = 0.010$) compared with patients who did not experience a cardiovascular event. Our findings are in agreement with Gosse *et al*. and Kuwajima *et al*., who studied the MBPS in hypertensive patients and found that the rising surge was significantly correlated with the LV mass index and the A/E ratio, which represents the diastolic function.[6,19]

Elevated serum uric acid level is associated with elevated systemic BP and the mechanism can be explained by the induction of oxidative stress state endothelial dysfunction and stimulation of the renin-angiotensin system.[22-24] This was reported by Turak *et al*., who found that there was a significant relationship between an increasing level of serum uric acid and increasing values of MBPS ($P < 0.0001$).[18] However, our finding did not show a significant association between serum uric acid and MBPS ($P < 0.79$). This may be due to the small number of patients in our study (81 patients) in comparison to 921 patients in Osman's study.

A few studies have reported the correlation between MBPS and level of HbA1c. Although our study showed that there

was a positive correlation between MBPS and the level of HbA1c, it was statistically insignificant ($P < 0.03$). A previous study by Yoda showed a significant positive correlation between MBPS and both HbA1c and TG ($P = 0.009$).[25] In the present study, by use of independent *t*-test, we found that there was no significant difference in the mean BP surge between diabetic and non-diabetic patients ($t = 1.19$, $P = 0.24$), which could be due to the fact that most of the diabetic patients enrolled in the study were under strict drug therapy and had a controlled blood glucose level.

CONCLUSION

Our study confirms previous reports that ABPM with measuring of MBPS is a feasible testing technique in patients with essential hypertension. MBPS can be used as a biomarker for hypertensive patients who are at risk of cardiovascular events.

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Conflicts of interest

There are no conflicts of interest.

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