Clinical and Experimental Hypertension

ISSN: 1064-1963 (Print) 1525-6006 (Online) Journal homepage: www.tandfonline.com/journals/iceh20

High morning blood pressure surge is associated with oxidative stress and paraoxonase 1 activity in newly diagnosed hypertensive patients

Onur Kaypaklı, Mustafa Gür, Hazar Harbalıoğlu, Taner Şeker & Şahabettin Selek

To cite this article: Onur Kaypaklı, Mustafa Gür, Hazar Harbalıoğlu, Taner Şeker & Şahabettin Selek (2016) High morning blood pressure surge is associated with oxidative stress and paraoxonase 1 activity in newly diagnosed hypertensive patients, Clinical and Experimental Hypertension, 38:8, 680-685, DOI: 10.1080/10641963.2016.1200602

To link to this article: https://doi.org/10.1080/10641963.2016.1200602

Published online: 09 Dec 2016.

CLINICAL AND EXPERIMENTAL HYPERTENSION
2016, VOL. 38, NO. 8, 680–685
http://dx.doi.org/10.1080/10641963.2016.1200602

Taylor & Francis
Taylor & Francis Group

High morning blood pressure surge is associated with oxidative stress and paraoxonase 1 activity in newly diagnosed hypertensive patients

Onur Kaypaklı[a], Mustafa Gür[a], Hazar Harbalıoğlu[a], Taner Şeker[a], and Şahabettin Selek[b]

[a]Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey; [b]Department of Biochemistry, Harran University Medical Faculty, Şanlıurfa, Turkey

ABSTRACT

Background: Both oxidative stress and morning surge (MS) of blood pressure (BP) were found to be closely related with cardiovascular and cerebrovascular diseases. We investigated the association between MS of BP and oxidative stress in newly diagnosed hypertensive patients. *Methods*: We prospectively included 237 newly diagnosed hypertensive patients in the present study (mean age: 51.6 ± 11.7 years). The patients were classified according to the extent of the sleep-through surge as follows: the top decile of sleep-through surge (>47.2 mmHg, $n = 27$; EMShigh group), versus all others ($n = 210$, EMSlow group). Total antioxidant capacity (TAC) and total oxidant status (TOS) levels were determined by using an automated measurement method. The oxidative stress index (OSI) was calculated as the ratio of TOS to TAC. Serum paraoxonase 1 (PON-1) activity was measured spectrophotometrically. *Results*: Patients in EMShigh group were found to have higher hs-CRP, TOS, and OSI values and lower TAC and PON-1 values ($p < 0.01$, for all). MS of BP was associated with hs-CRP, PON-1, TOS, TAC, and OSI levels in bivariate analysis. Multivariate linear regression analysis showed that MS of BP was significantly associated with PON-1($\beta = -0.206$, $p < 0.001$), OSI ($\beta = 0.602$, $p < 0.001$) and hs-CRP ($\beta = 0.210$, $p < 0.001$). *Conclusion*: Present study shows that OSI is increased and antioxidant PON-1 activity is decreased in patients with enhanced MS of BP. There is a close association between high MS of BP and oxidative stress markers in newly diagnosed hypertensive patients.

ARTICLE HISTORY
Received 6 March 2016
Revised 7 May 2016
Accepted 25 May 2016
Published online
21 November 2016

KEYWORDS
Ambulatory blood pressure; hypertension; oxidative stress; morning blood pressure surge; PON-1

Introduction

Hypertension (HT) causes target organ damage by the direct physical effect of increased blood pressure as well as the active promotion of atherosclerosis and thrombogenesis (1,2). There is a clear diurnal variation of the onset time of cardiovascular events. Cardiovascular events occur most frequently in the morning. Ambulatory monitoring has revealed that blood pressure (BP) tends to display a similar diurnal variation with morning blood pressure surge (3). This finding suggested that an increased morning surge (MS) of BP might have a role in the occurrence of cardiovascular events. On the other hand, the studies investigating the association between cardiovascular events and MS of BP have produced conflicting results.

Oxidative stress plays a critical role on the pathogenesis of atherosclerosis. Moreover, increased oxidative stress is associated with both cardiovascular and cerebrovascular diseases. High-density lipoprotein (HDL) cholesterol exerts cardioprotective properties through its antioxidant activity and antiinflammatory effects, which is largely maintained by serum paraoxonase 1 (PON-1) (4). PON-1 protects lipoproteins against oxidative modification and to hydrolyze hydrogen peroxide, a major reactive oxygen species (ROS) produced under conditions of inflammation and atherosclerosis (4). Oxidative stress triggers pro-inflammatory, prothrombotic, proliferative, and vasoconstrictor mechanisms related to abnormal endothelial function (5). As oxidative stress is known to play important roles in the pathogenesis of cardiovascular events that occur most frequently in the morning, it is reasonable to expect an association between oxidative stress and MS of BP. We aimed to investigate the association between MS of BP and oxidative stress markers such as OSI and PON-1 activity in newly diagnosed hypertensive patients.

Methods

Study populations

We prospectively included 237 patients with newly diagnosed essential HT according to office BP measurements between January 2014 and July 2014. Patients with severe liver or renal disease, secondary or malignant HT, heart failure, patients with known coronary artery disease and diabetes, the signs and symptoms of coronary artery disease (CAD) (such as chest pain, ST depression or elevation, positive non-invasive stress test), cerebrovascular disease, valve disease, atrial fibrillation, major non-cardiovascular diseases such as infectious or inflammatory diseases, hematological disease, neoplastic disease were excluded from the study. Patients with suspicion (excessive daytime sleepiness, choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration that are not better explained by other factors) of having sleep apnea syndrome (SAS) were also excluded from the study. Of 288 patients having office BP measurement ≥140/90 mmHg, 51 patients

CONTACT Onur Kaypakli onurkaypakli@hotmail.com Department of Cardiology, Adana Numune Training and Research Hospital, Adana 01170, Turkey.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/iceh.

were excluded because their BP recordings were normal at ambulatory blood pressure monitoring (ABPM). They were not accepted as hypertensive patients and thought to have white coat HT. Measurements were obtained from 237 patients with newly diagnosed essential HT (mean age 51.6 ± 11.7 years; male/female 84/153). Patients taking antioxidant drugs such as statins, diuretics, angiotensin-converting enzyme inhibitors (captopril, zofenopril), beta-blocking agents (carvedilol, nebivolol), vitamins (such as E and C), and other antihypertensive drugs were excluded from the study. No dietary variation was present between the groups. Patients taking xenobiotics and alcohol were also excluded from the study. The Local Ethics Committee approved the study protocol, and each participant provided written informed consent.

After assessment of detailed medical history and a complete physical examination, the baseline characteristics of patients including age, sex, hypertension, current smoking status, family history of CAD, body mass index (BMI), and medications were recorded for all patients. Electrocardiogram, routine laboratory tests, echocardiographic examination and noninvasive ambulatory BP monitoring were applied to all patients.

Echocardiography

Standard two-dimensional and Doppler echocardiography were performed using a commercially available echocardiographic machine (Vivid 7R GE Medical System, Horten, Norway). Left ventricular (LV) end-diastolic diameters (LVDd), end-diastolic interventricular septal thickness (IVSth) and end-diastolic left ventricular posterior wall thickness (PWth) were measured at end-diastole according to established standards of the American Society of Echocardiography (6). LV ejection fraction (EF) was determined by the biplane Simpson's method (7). Left ventricular mass (LVM) was calculated using the Devereux formula (8): LVM = 1:04[(LVDd+IVSth+PWth)3 – (LVDd)3] – 13.6.

Office blood pressure measurements

Systolic BP (SBP) and diastolic BP (DBP) recordings were performed by a physician by using a mercury sphygmomanometer with appropriate-sized cuffs. Office BP measurements were done by the same physician. Diastolic BP was determined by using phase V. Following the guidance of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP, at least three separate measurements on three different days (9) were performed and the mean value was determined as the office BP.

Ambulatory blood pressure measurements

Noninvasive 24 h ABPM was performed with a portable, compact digital recorder (Tracker NIBP2, Delmar Reynolds Ltd., Hertford, UK) on a day of typical activity and analyzed using customized analytical software (Delmar Reynolds Medical Inc., Model 2169, Hertford, UK). The device was programmed to inflate and record BP at pre-specified intervals (15-min intervals from 6 am to midnight, and at 30-min intervals from midnight to 6 am), which provided approximately 80 BP recordings during the 24 h period. Patients were instructed to note awake and asleep intervals to a diary. Daytime (awake period), nighttime (asleep period), and 24-h mean systolic and diastolic BP, BP load, heart rate, weighted standard deviation (SD) of 24-h BP as an index of BP variability were evaluated. When successful readings exceeded at least 80% of the total readings programmed for the testing period, the recording was considered valid and satisfactory. Recordings with systolic BP > 260 or <70 mmHg or if diastolic BP was >150 or <40 mmHg and pulse pressure was >150 or <20 mmHg were excluded.

Diagnosis of hypertension

In each participant, BP was measured on at least three separate days after 15 min of sitting comfortably and the mean value was determined as the office BP. Participants who had systolic BP ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg in the office setting, and an average 24 h systolic BP > 130 mmHg and/or diastolic BP > 80 mmHg, an average daytime systolic BP > 135 mmHg and/or diastolic BP > 85 mmHg or an average nighttime systolic BP > 125 mmHg and/or diastolic BP > 75 mmHg in 24 h ABPM were diagnosed as hypertensive (10). In addition, the participants who had a <10% reduction in BP from the daytime to the nighttime period were defined as non-dipper hypertensive (NDH), and the participants who had a BP reduction ≥10% from the daytime to the nighttime period were defined as dipper hypertensive (DH), and the participants who had a BP reduction ≥20% from the daytime to the nighttime period were defined as extreme DH (11).

Morning surge of blood pressure

To calculate the MS of BP, we detected the awake and asleep intervals from the participants' diary. We used sleep-through morning surge of BP. The MS of BP was calculated as the difference between the mean systolic BP during the 2 h after awaking (four BP readings) and the mean systolic BP during the 1 hour that included the lowest sleep BP (12,13). There is no consensus on a cut-off value for the morning BP surge. As the cut-off value for identifying the top decile was 47.2 mmHg, we subclassified the patients according to the extent of the sleep-through surge as follows: the top decile of sleep-through surge (>47.2 mmHg, n = 27; EMShigh group), versus all others (n = 210, EMSlow group).

Blood sampling

Venous blood samples were obtained at (polyclinic) admission. Samples were taken from cubital vein into blood tubes and immediately stored on ice at 4°C. The serum was then separated from the cells by centrifugation at 3000 rpm for 10 min. Serum samples were stored at −80°C until analysis of lipid parameters, PON-1 activity, total oxidant status (TOS), and total antioxidant capacity (TAC).

Blood counts were measured by a Sysmex K-1000 (Block Scientific, Bohemia, New York) autoanalyzer within 5 min of sampling. Plasma triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, and creatinine concentrations were measured with an automated chemistry analyzer (Abbott Aeroset, Minnesota, USA) using commercial kits (Abbott).

Measurement of serum paraoxonase-1 (PON-1) activity

Measurement of serum PON-1 activity was performed in the absence of NaCl (basal activity). The rate of paraoxon hydrolysis (diethyl-*p*-nitrophenylphosphate) was measured by monitoring the increase of absorbency at 412 nm at 37°C. The amount of generated *p*-nitrophenol was calculated from the molar absorptivity coefficient at pH 8, which was 17,000 M^{-1} cm^{-1} (14). PON-1 activity was expressed as U L^{-1} serum. The coefficient of variation (CV) for measurement of serum PON activity was 2.1%.

Measurement of total oxidant status (TOS), total antioxidant capacity (TAC), and oxidative stress index (OSI)

The TAC and TOS levels of serum were measured as described previously (15,16). The oxidative stress index (OSI) was calculated as the ratio of TOS to TAC. The unit for total antioxidative capacity of plasma, was expressed as mmol Trolox equivalent L^{-1}, and the total oxidant status of plasma as the micromolar hydrogen peroxide equivalent per liter (mmol H_2O_2 Eq L^{-1}).

Statistical analysis

All analyses were conducted using SPSS 17.0 (SPSS for Windows 17.0, Chicago, IL, USA). Comparison of categorical variables between the groups was performed using the chi-square (χ^2) test. Analysis of normality was performed with the Kolmogorov–Smirnov test. Independent samples *t*-test was used in the analysis of continuous variables. Multivariate, stepwise backward conditional logistic regression analysis was used to determine the independent predictors of MS of BP. All significant parameters in the univariate analysis were selected in the multivariate model. A receiver operator characteristic curve analysis was carried out to identify the optimal cut-off point of OSI and PON-1 to detect morning surge of blood pressure. The value of the area under the curve was calculated as a measure of the accuracy of the test. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A comparison between the baseline demographics and laboratory and echocardiographic findings is shown in Table 1. There were no statistically significant difference in demographic and echocardiographic parameters ($p > 0.05$, for all). Patients in EMShigh group were found to have higher hs-CRP, TOS, and OSI ($p < 0.01$, for all) values and lower TAC and PON-1 values ($p < 0.01$, for all).

Ambulatory blood pressure measurements

Comparison of ambulatory blood pressure measurement variables is shown in Table 2. There were no statistically significant difference in ambulatory blood pressure measurement variables except of MS of BP ($p > 0.05$, for all).

Table 1. Baseline characteristics of groups.

Variables	EMS_{high} Group (n = 27)	EMS_{low} Group (n = 210)	*p*-value
Baseline findings			
Age (year)	49.7 ± 13.4	51.9 ± 11.4	0.371
Gender (male)	8 (29.6%)	76 (36.2%)	0.329
BMI (kg/m^2)	31.3 ± 5.3	30.9 ± 5.7	0.700
Heart rate (b/m)	79.6 ± 12.8	79.6 ± 11.9	0.977
Smoking, *n* (%)	8 (29.6%)	52 (24.8%)	0.367
Laboratory findings			
Glucose (mg/dl)	97.0 ± 6.1	94.2 ± 9.0	0.125
Total cholesterol (mg/dl)	205.8 ± 43.6	215.7 ± 44.5	0.275
Triglyceride (mg/dl)	161.7 ± 63.8	181.5 ± 89.4	0.267
HDL cholesterol (mg/dl)	48.2 ± 15.2	47.0 ± 11.0	0.609
LDL cholesterol (mg/dl)	142.0 ± 39.2	146.4 ± 34.7	0.542
Creatinin (mg/dl)	0.85 ± 0.27	0.83 ± 0.37	0.764
Hemoglobin (mg/dl)	13.6 ± 1.6	13.9 ± 1.8	0.428
HsCRP (mg/dl)	0.83 ± 0.18	0.69 ± 0.21	**0.001**
TAC	0.72 ± 0.23	0.97 ± 0.24	**<0.001**
TOS	34.8 ± 10.2	21.7 ± 8.9	**<0.001**
OSI	52.6 ± 20.1	25.2 ± 15.3	**<0.001**
PON-1	82.2 ± 40.1	115.7 ± 54.1	**0.002**
Echocardiographic findings			
LAD (mm)	3.72 ± 0.39	3.66 ± 0.40	0.472
LVID (mm)	4.6 ± 0.5	4.5 ± 0.5	0.744
LVM	207.2 ± 65.1	192,5 ± 47.0	0.146
Ejection fraction, %	60.8 ± 4.0	61.8 ± 4.9	0.297

Abbreviations: EMS, early morning surge; BMI, body mass index; HDL, high density lipoprotein; hs-CRP, high sensitive C reactive protein; LAD, left atrial diameter; LDL, low-density lipoprotein; LVID, left ventricle internal diameter; LVM, left ventricle mass; TOS, total oxidant status; TAC, total antioxidant capacity; OSI, oxidative stress index.
Bold values are statistically significant.

Table 2. Office and ambulatory blood pressure measurements.

Variables	EMS_{high} group	EMS_{low} group	*p*-value
Blood pressure measurements (mmHg)			
Office SBP	157.4 ± 20.7	160.4 ± 18.8	0.439
Office DBP	95.1 ± 9.8	98.0 ± 9.7	0.152
Average 24-h SBP	137.9 ± 9.3	137.6 ± 9.2	0.874
Average 24-h DBP	85.7 ± 7.2	84.4 ± 7.9	0.453
Average daytime SBP	143.0 ± 8.0	144.8 ± 8.9	0.315
Average daytime DBP	90.9 ± 6.3	91.2 ± 6.8	0.920
Average nighttime SBP	132.9 ± 14.0	130.5 ± 11.5	0.316
Average nighttime DBP	80.3 ± 10.0	77.8 ± 10.5	0.234
Average morning SBP	145.1 ± 8.0	144.9 ± 8.7	0.545
Average morning DBP	92.0 ± 11.5	91.6 ± 9.4	0.660
Morning BP surge	56.9 ± 9.0	20.5 ± 14.0	**<0.001**
Dipper hypertension, *n* (%)	8 (29.6%)	90 (42.9%)	0.134
Non-dipper hypertension, *n* (%)	17 (63.0%)	106 (50.5%)	0.154
Extreme dipper hypertension, *n* (%)	2 (7.4%)	14 (6.7%)	0.566

Abbreviations: EMS, early morning surge; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure.
Bold values are statistically significant.

Bivariate and multivariate relationships of MS of BP (Table 3)

MS of BP was associated with hs-CRP ($r = 0.264$, $p < 0.001$), PON-1 ($r = -0.510$, $p < 0.001$), TOS ($r = 0.665$, $p < 0.001$), TAC ($r = -0.640$, $p < 0.001$), and OSI levels ($r = 0.729$, $p < 0.001$) in bivariate analysis.

Table 3. Bivariate and multivariate relationships of MS of BP.

Variables	Pearson correlation coefficient	*p*-value	Standardized β-regression coefficients	*p*-value
Hs-CRP	0.264	**<0.001**	0.210	**<0.001**
PON-1	−0.510	**<0.001**	−0.206	**<0.001**
TOS	0.665	**<0.001**	–	–
TAC	−0.640	**<0.001**	–	–
OSI	0.729	**<0.001**	0.602	**<0.001**

Abbreviations: TOS, total oxidant status; TAC, total antioxidant capacity; OSI, oxidative stress index; hs-CRP, high sensitive C reactive protein.
Bold values are statistically significant.

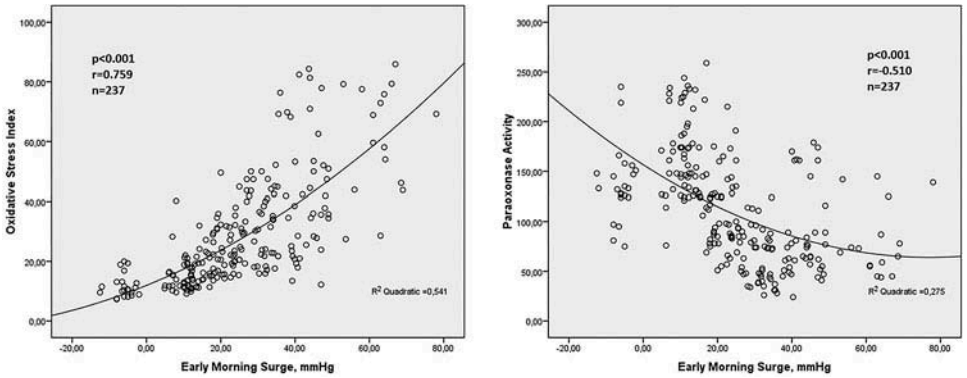

Figure 1. (a) Relationship between MS of BP and OSI. (b) Relationship between MS of BP and PON-1.

Multivariate linear regression analysis showed that MS of BP was significantly associated with PON-1 ($\beta = -0.206$, $p < 0.001$), OSI ($\beta = 0.602$, $p < 0.001$), and hs-CRP ($\beta = 0.210$, $p < 0.001$). Relationships between MS of BP with OSI and PON-1 are shown in Figure 1a and b, respectively.

ROC curve analysis

The cutoff value of OSI obtained by the ROC curve analysis was 35.5 arbitrary unit for the prediction of MS of BP (sensitivity: 81.5%, specificity: 81.5%). The area under the curve (AUC) was 0.868 (95% CI: 0.798–0.937, $p < 0.001$).

The cutoff value of PON-1 activity obtained by the ROC curve analysis was 78.5 U L^{-1} for the prediction of MS of BP (sensitivity: 70.0%, specificity: 67.0%). The area under the curve (AUC) was 0.692 (95% CI: 0592–0.793, $p < 0.001$).

The ROC curves of OSI and PON-1 for predicting high MS of BP were shown in Figure 2a and b, respectively.

Discussion

Oxidative stress markers and morning surge (MS) of blood pressure (BP) were found to be closely related to cardiovascular and cerebrovascular diseases. (13,17–19). To the best of our knowledge the present study is the first in the literature that evaluates the relation between oxidative stress, PON-1 activity and MS of systolic BP in newly diagnosed hypertensive patients. The main finding of this study is that oxidative stress markers are increased and antioxidant PON-1 activity is decreased in patients with enhanced MS of systolic BP.

ROS include the superoxide anion (O_2^-), hydroxyl (OH^-) free radicals, and non-radicals, such as H_2O_2. The primary ROS molecule O_2^- can be generated by several enzyme systems, including the mitochondrial electron-transport chain, COXs (cyclo-oxygenases), lipoxygenases, cytochrome P450 reductases, xanthine oxidase, NOS, and NADPH oxidases (20). There is a balance between oxidative effects of free radicals and antioxidants in human plasma. When the level of ROS exceeds the level of antioxidant defense systems, oxidative stress occurs. The measurement of OSI reflects the oxidative status of human plasma (21). An HDL associated protein PON-1 has been found to play an important role in the maintenance of the low oxidative state (22). PON-1 has been found to play an important role in hydrolysis of hydrogen peroxides, which is a major reactive oxygen species at oxidative modification of LDL (23). PON-1 protects LDL from oxidative modification, which makes it highly antiatherogenic. Therefore, an association between PON-1 levels and atherosclerosis risk was revealed by several studies (24,25). Oxidative stress triggers proinflammatory, prothrombotic, proliferative, and vasoconstrictor mechanisms related to abnormal endothelial function (26). So, the combination of an excessive production of reactive oxygen species with an impaired antioxidant defense capacity leading to endothelial dysfunction may facilitate the development and progression of atherosclerotic cerebrovascular disease. Findings from recent clinical studies suggest that this mechanism can be important in patients with acute or chronic cerebrovascular diseases (27).

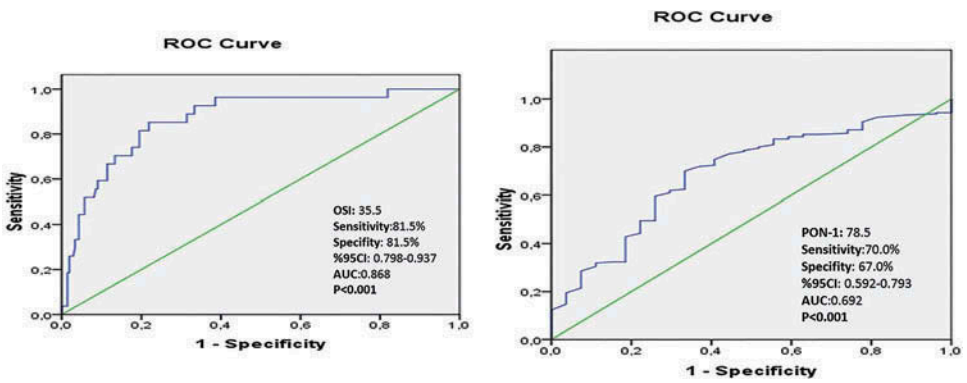

Figure 2. (a) The ROC curve analysis of OSI for predicting high MS of BP. (b) The ROC curve analysis of PON-1 for predicting high MS of BP.

It has been considered that the MS of BP may be particularly harmful, because cardiovascular and cerebrovascular events occur most frequently in the morning (13,28–30). We used sleep-through morning surge of BP. The preawakening MS of BP, which is defined as the difference between the mean BP during the 2 h after waking and the mean BP during the 2 h before waking, has been shown to have less power for the prediction of cardiovascular events than sleep-through morning BP surge (13).

The rate of the MS of BP in 24-hour ABPM was found to be greater in hypertensive patients than normotensive participants. On the other hand, the studies investigating the association between cardiovascular events and MS of BP have produced conflicting results. While some studies demonstrated MS of BP to be an independent risk factor for cardiovascular and cerebrovascular events (18,19), other studies did not (31,32). It was previously reported that in elderly hypertensive patients a high morning BP surge was associated with increased stroke risk (33). The hour of awakening, rather than the hour of the day, was found to be most closely related to the occurrence of vascular events (34,35). Pierdomenico et al. previously demonstrated that MS of BP was independent of risk of stroke events (19). The associations of MS of BP with stroke and coronary events were found to be independent of BP level and weighted standard deviation of 24-hour blood pressure at dipper patients in the study of Pierdomenico et al. (18,19). In the study of Kario K et al., the stroke events were found to be significantly more likely to occur in the morning (13). Increased rate of cerebrovascular events in morning hours may even be observed in high-risk hypertensive patients with well-controlled home and ambulatory blood pressure (3).

An exaggerated morning BP surge may advance vascular remodeling from the larger arteries to the small resistance vessel through increased mechanical pressure and shear stress of an exaggerated fluctuation of blood flow on the vessel wall (36). Plaques biopsied from patients with hypertension with an increased morning BP surge had increased levels of macrophages, T lymphocytes, ubiquitin–proteasome activity, tumor necrosis factor-α, and matrix metalloproteinase-9 (37). If we take into account of greater activity of the sympathetic and renin–angiotensin–aldosterone systems in the morning, the effect of morning BP on endothelial cells and subsequent vascular damage can be thought to be greater than other periods of the day.

Because oxidative stress and inflammation are known to play important roles in the pathogenesis of cardiovascular events that occur most frequently in the morning, it is logical to expect an association between oxidative stress and MS of BP. It has been suggested that in hypertensive patients with MS of BP there is an increased risk of cerebrovascular events (33), and that oxidative stress is one of the causes of cerebrovascular stroke (13,17,28). Polymorphonuclear leukocytes (PMNs) and mononuclear cells (MNCs) are one of the basic sources of ROS. PMNs and MNCs are known to be activated by hypertension to release ROS, including hydrogen peroxide, contributing to endothelial damage and cardiovascular disease (19,38–40). When oxidative stress is increased, MNCs induce adhesion to the endothelium, which results in atherosclerotic diseases (41). MS of BP may be considered to be inducing effects of hypertension that activates release of ROS. Further molecular studies are needed to verify the effect of MS of BP on ROS accumulation.

Inflammatory mechanism is an important factor for cardiovascular events. Hypertensive patients with exaggerated morning BP surge have been found to have higher levels of systemic inflammatory markers, such as high-sensitive C-reactive protein and interleukin-6, than those without surge (36). Shimizu et al. (42) reported an association between hs-CRP and MS of BP. We also found a significant association between hs-CRP and MS of BP.

Cinical implication

We demonstrated an association between MS of BP and PON-1 activity and also between MS of BP and OSI. OSI is increased and PON-1 activity decreased in newly diagnosed hypertensive patients with enhanced MS of systolic BP. So, our findings suggest that serum PON-1 activity and oxidative stress markers may be used along with MS of BP to detect newly diagnosed hypertensive patients without known cardiovascular and cerebrovascular disease who are in high risk of cerebrovascular diseases and who can benefit from pharmacological or interventional treatment strategies. Additionally, increasing PON-1 activity and decreasing oxidative stress markers could be an important target for future pharmacological agents to decrease future cardiovascular and cerebrovascular risk. However, the most important thing is to decrease the BP levels including morning BP, nocturnal BP, and MS for preventing cardiovascular events.

Study limitations

Coronary angiography was not performed on the patients. However, coronary artery disease has been excluded according to treadmill exercise test, ECG, and medical history. PON-1 has two coding region amino acid polymorphisms, one at position 55 and the other at position 192 (26). The Q192R polymorphism has such a significant effect on PON-1 activity. It is possible, but not advisable, to use PON-1 activity within a 192 genotype/phenotype (e.g. Q/Q, Q/R, or R/R). In this study, the PON-1 phenotype or genotype was not determined (43,44). Like our study, in most studies, PON-1 activity was measured with paraoxon as a substrate, while diazoxon was used on very few occasions (45,46). It has been suggested that serum PON-1 activity was a better predictor of the risk of cardiovascular diseases than the PON-1 genotype.

In conclusion, oxidative stress calculated with OSI is increased and antioxidant PON-1 activity is decreased in newly diagnosed hypertensive patients with enhanced MS of systolic BP. Future studies are needed to verify collective efficacy of oxidative stress markers and MS of BP to detect future cerebrovascular and cardiovascular risk in newly diagnosed hypertensive patients without known cardiovascular and cerebrovascular disease.

References

1. Lip GY. Target organ damage and the prothrombotic state in hypertension. Hypertension 2000; 36:975–7.
2. Yıldız G, Hur E, Ozcicek A, et al. The mean platelet volume and atherogenic index of plasma in nondipper normotensive individuals compared to dippers. Clin Exp Hypertens 2013;35:35–9.
3. Kario K. Essential manual of 24-hour blood pressure management from morning to nocturnal hypertension. Wiley-Blackwell: London, UK; 2015; pp. 1–138.
4. Gur M, Turkoglu C, Taskın A et al. Paraoxonase-1 activity and oxidative stress in patients with anterior ST elevation myocardial infarction undergoing primary percutaneous coronary intervention with and without no-reflow. Atherosclerosis 2014;234 415–420.
5. Becker LB. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res 2004;61:461–470.
6. Lang RM, Bierig M, Devereux RB et al; Chamber Quantification Writing Group. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and The Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
7. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
8. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55:613–8.
9. Stergiou GS, Salgami EV. World Health Organization-International Society of Hypertension (WHO-ISH); USA Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-7); European Society of Hypertension-European Society of Cardiology (ESH-ESC). New European, American and International guidelines for hypertension management: agreement and disagreement. Expert Rev Cardiovasc Ther 2004;2:359–68.
10. Verdecchia P, Schillaci G, Porcellati C. Dippers versus non-dippers. J Hypertens Suppl 1991;9:42–8.
11. Kario K. Orthostatic hypertension - a new haemodynamic cardiovascular risk factor. Nat Rev Nephrol 2013;9:726–738.
12. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med 2006;354:2368–74.[CrossRef]
13. Kario K, Pickering TG, Umeda Y et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003;107:1401–6.
14. Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 1983;35:1126–38.
15. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004;37:112–9.
16. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103–11.
17. Gosse P, Lasserre R, Minifie C, et al. Blood pressure surge on rising. J Hypertens 2004;22:1113–1118.
18. Pierdomenico SD, Pierdomenico AM, Tommaso RD et al. Morning blood pressure surge, dipping and risk of coronary events in elderly treated hypertensive patients. Am J Hypertens. 2016;Jan;29(1):39–45
19. Pierdomenico SD, Pierdomenico AM, Cuccurullo F. Morning blood pressure surge, dipping, and risk of ischemic stroke in elderly patients treated for hypertension. Am J Hypertens 2014;27:564–570.
20. Miller AA, Budzyn K, Sobey CG. Vascular dysfunction in cerebrovascular disease: mechanisms and therapeutic intervention. Clinical Science 2010;119, 1–17
21. Pitocco D, Tesauro M, Alessandro R, et al. Oxidative stress in diabetes: implications for vascular and other complications. Int J Mol Sci. 2013;14(11):21525–21550.
22. Aviram M, Rosenblat M, Bisgaier CL et al. Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 1998;101:1581–1590.
23. Sarkar PD, Madhusudhan, TMS B. Association between paraoxonase activity and lipid levels in patients with prematüre coronary artery disease. Clin Chim Acta 2006;373:77–81.
24. Tartan Z, Orhan G, Kasikcioglu H et al. The role of paraoxonase (PON) enzyme in the extent and severity of the coronary artery disease in type-2 diabetic patients. Heart Vessels 2007;22:158–164.
25. Gur M, Caylı M, Ucar H et al. Paraoxonase (PON1) activity in patients with subclinical thoracic aortic atherosclerosis. Int J Cardiovasc Imaging 2014;30:889–895.
26. Mackness MI, Mackness B, Durrington PN. Paraoxonase and coronary heart disease. Atheroscler Suppl 2002;3:49–55.
27. Zalba G, Fortuño A, San José G et al. Oxidative stress, endothelial dysfunction and cerebrovascular disease. Cerebrovasc Dis 2007;24 Suppl 1:24–9.
28. Verdecchia P, Angeli F, Mazzotta G et al. Day-night dip and early-morning surge in blood pressure in hypertension: prognostic implications. Hypertension 2012;60:34–42.
29. White WB. Relevance of blood pressure variation in the circadian onset of cardiovascular events. J Hypertens Suppl 2003;21:9–15.
30. Kario K. Morning surge in blood pressure and cardiovascular risk: evidence and perspectives. Hypertension 2010;56:765–73.
31. Kario K. Prognosis in relation to blood pressure variability: pro side of the argument. Hypertension 2015;65:1163–1169.
32. Asayama K, Wei FF, Hara A et al. Prognosis in relation to blood pressure variability: con side of the argument. Hypertension 2015;65:1170–1179.
33. Muller JE, Ludmer PL, Willich SN et al. Circadian variation in the frequency of sudden cardiac death. Circulation 1987;75:131–138.
34. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733–743.
35. Elliott WJ. Circadian variation in the timing of stroke onset: a metaanalysis. *Stroke* 1998;29:992–996.
36. Kario K. Vascular damage in exaggerated morning surge in blood pressure. Hypertension 2007;49:771–772.
37. Marfella R, Siniscalchi M, Portoghese M, et al. Morning blood pressure surge as a destabilizing factor of atherosclerotic plaque: role of ubiquitinproteasome activity. Hypertension 2007;49:784–791.
38. Turak O, Afsar B, Ozcan F et al. Relationship between elevated morning blood pressure surge, uric acid, and cardiovascular outcomes in hypertensive patients. J Clin Hypertens (Greenwich) 2014;16:530–535.
39. Amodeo C, Guimaraes GG, Picotti JC, et al. Morning blood pressure surge is associated with death in hypertensive patients. Blood Press Monit 2014;19:199–202.
40. Metoki H, Ohkubo T, Kikuya M et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. Hypertension 2006;47:149–154.
41. Amici A, Cicconetti P, Sagrafoli C et al. Exaggerated morning blood pressure surge and cardiovascular events. A 5-year longitudinal study in normotensive and well-controlled hypertensive elderly. Arch Gerontol Geriatr 2009;49:105–109.
42. Shimizu M, Ishikawa J, Yano Y et al. The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events. Atherosclerosis 2011;219:316–321.
43. Mackness B, Davies GK, Turkie W et al. Paraoxonase status in coronary heart disease. Are activity and concentration more important than genotype? Arterioscler Thromb Vasc Biol 2001;21:1451–1457.
44. Jarvik GP, Rozek LS, Brophy VH et al. Paraoxonase (PON1) phenotype is a better predictor of vascular disease than is PON1 (192) or PON1(55) genotype. Arterioscler Thromb Vasc Biol 2000;20:2441–2447.
45. Costa LG, Vitalone A, Cole TB, Furlong CE. Modulation of paraoxonase (PON1) activity. Biochem Pharmacol 2005;69:541–550
46. Gupta N, Binu KB, Singh S et al. Low serum PON1 activity: an independent risk factor for coronary artery disease in North-West Indian type 2 diabetics. Gene 2012;498:13–19.