# Relationship Between Elevated Morning Blood Pressure Surge, Uric Acid, and Cardiovascular Outcomes in Hypertensive Patients

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Early morning blood pressure surge (MBPS) is a risk factor for cardiovascular events (CVEs), but the relationship with uric acid is not well understood. The authors aimed to determine the association between MBPS and increased uric acid and the effect of elevated MBPS and uric acid combination on CVEs. A total of 921 patients underwent 24-hour ambulatory blood pressure monitoring and were followed for a median of 40 months. During this period, 103 (11.2%) CVEs occurred. There was a significant relationship between increasing quartiles of serum uric acid level and increasing values of MBPS ($P<.0001$). Patients in the highest quartile stratified by elevated MBPS and serum uric acid level had a 3.55 odds of major CVE compared with patients in the lowest quartile. Serum uric acid is associated with MBPS and development of new CVEs. *J Clin Hypertens (Greenwich).* 2014;16:530–535. ©2014 Wiley Periodicals, Inc.

Blood pressure (BP) is significantly elevated upon awakening, a phenomenon recognized as the morning blood pressure surge (MBPS). Usually this indicates a normal physiological response to changes in physical activity and is a constitutive part of the circadian BP rhythm.[1] However, BP values above the MBPS threshold are associated with target organ damage, including left ventricular hypertrophy, proteinuria, and stroke.[2,3] Various factors are associated with increased MBPS, including environmental factors,[4] age and sex,[5,6] physical activity,[7] sympathetic nervous tone,[8] renin-angiotensin system,[9] arterial stiffness,[10] nondipping status,[11] and endothelial dysfunction.[12] However, the mechanisms accounting for MBPS remain conjectural and the exact etiopathogenic mechanisms are not fully known.[13]

An elevated serum uric acid (SUA) level is strongly associated with hypertension.[14] An elevated SUA level predicts the development of hypertension and correlate with BP, especially for nondipping BP.[15,16] Experimental hyperuricemia in rats also results in raised BP, and the mechanism has been shown to be caused by the induction of oxidative stress,[17] endothelial dysfunction, and activation of the renin-angiotensin system,[18] coupled with subtle microvascular and inflammatory changes in the kidney.[19] Pilot studies have also reported that lowering uric acid level can result in improvement in BP in both adolescents and adults with hyperuricemia.[20,21] Since SUA peaks in the early morning,[22] we hypothesized that morning SUA might relate to the early MBPS.

Thus, we designed this study to investigate (1) whether SUA and MBPS are related to each other and (2) the role of elevated SUA level and MBPS, single or in combination, for major cardiovascular events (MACEs) including death, stroke or transient ischemic attack, and cardiac events (sudden death, fatal and nonfatal myocardial infarction, and coronary revascularization).

## MATERIALS AND METHODS

### Study Population

In this observational cohort study we enrolled a total of 921 consecutive patients who visited a outpatient hypertension clinic and underwent 24-hour ambulatory BP monitoring (ABPM) using validated devices between January 2008 and December 2011. All included patients had essential hypertension, either untreated or taking antihypertensive therapy. During each ABPM recording, patients were required to continue their usual daily activities, avoiding only unusual physical exercises or behavioral challenges, and to mark in a diary their main activities, including the time of meals, bed rest, or sleep and awakening times. Patients with chronic liver disease; chronic kidney disease (estimated Chronic Kidney Disease [CKD] Epidemiology Collaboration [CKD-EPI] glomerular filtration rate [GFR] <60 mL/min/1.73 $m^2$); obvious ongoing illness (eg, malignancy or infection) at baseline; history of gout, stroke (including transient ischemic attacks), arrhythmias (including

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atrial fibrillation), obstructive sleep apnea, and heavy alcohol intake; night workers and patients who were taking medications known to influence SUA levels (eg, allopurinol, nonsteroidal anti-inflammatory drugs, vitamin use) were excluded from the cohort. Estimated GFR (eGFR) were calculated via the CKD-EPI equation. The study complied with the Declaration of Helsinki, the study protocol was approved by the Yuksek Ihtisas Education, and Research Hospital ethics committee and informed consent was obtained from all participants.

Patients' blood tests and clinical data collection were performed on the day of application of ABPM device. All blood samples were obtained from patients in the morning after 12 hours of fasting for measurement of SUA, fasting plasma glucose (FPG), serum albumin, total serum cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol. Diabetes mellitus was defined according to international guidelines. Smokers were defined as current smokers. Body mass index was calculated as weight (kg)/height ($m^2$).

### 24-Hour ABPM

The noninvasive 24-hour ABPM reading device (Mobil-O-Graph; IEM GmbH, Stolberg, Germany) used has been described elsewhewre.[23] Briefly, the readings were recorded at 20- and 30-minute intervals in the daytime and at nighttime, respectively. The respective daytime and nighttime hours were defined using certain time intervals, which ranged from 6 AM to10 PM and from 10 PM to 6 AM. Sleep and wake periods were determined on the basis of diary activity reports. Interactive software was utilized to assess the recordings. Any patient lacking ≥20% of the measurements was excluded from the study. The mean values of daytime, nighttime, and 24-hour systolic BP (SBP) and diastolic BP (DBP) were calculated for each patient on the basis of hourly averages of ambulatory BP recordings. We defined morning BP surge as the morning SBP (averaged SBP for 2 hours just after waking up) minus the lowest nocturnal SBP by using ABPM after the run-in period (sleep through morning surge as suggested by Kario and colleagues).[24]

Participants who showed a nocturnal fall of ≥10% in SBP were considered dippers. Likewise, a patient whose nocturnal SBP fell by <10% or even rose was defined as a nondipper. Office SBP and DBP values were also recorded. Office BP measurements were performed by the same person, following the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure on at least two separate occasions on different days.[25]

### Follow-Up and Endpoints

The patients' medical records or other source documents were reviewed periodically after performing the 24-hour ABPM for the occurrence of cardiovascular outcomes. All included patients were followed up for time-to-event analysis until occurrence of MACEs including death, stroke or transient ischemic attack, and cardiac events (sudden death, fatal and nonfatal myocardial infarction, and coronary revascularization). MACEs were recorded by reviewing outpatient clinic visits in the medical records and telephone contact if such information was not available. We also checked deaths from the national death report system regularly (www.obs.gov.tr).

### Statistical Analysis

Sex-specific quartiles of uric acid were defined as follows for men: quartile 1: ≤4.8 mg/dL; quartile 2: 4.9–5.4; quartile 3: 5.5–6.4; and quartile 4: >6.4; and for women: quartile 1: ≤4.8 mg/dL; quartile 2: 4.9–5.2; quartile 3: 5.5–6.0; and quartile 4: >6.0. Analysis of variance with Tukey-Kramer *P*-value adjustments were used to compare characteristics across quartiles of uric acid. Adjusted *P* values <.05 were considered significant. Chi-square or Fisher exact test were used to test categorical variables across quartiles of uric acid. Cox regression was used to determine the relationship of MBPS, uric acid, and sex-specific quartiles of uric acid to the hazard of MACEs. Results are reported as hazard ratio (HR) (95% confidence interval [CI]). *P*<.05 was considered significant. HR represents a 1 unit change in continuous variables; thus, the HR for uric acid as a continuous variable is the HR for a 1-mg/dL increase in uric acid.

## RESULTS

Data regarding uric acid, MBPS, and MACEs were available in 921 patients, of whom 103 (11.2%) had MACEs. There were 420 (45.6%) women and 501 (54.4%) men. A total of 160 patients (17.4%) had diabetes, 204 (22.2%) had a history of smoking, 372 (40.4%) were taking antihypertensive medications, 8 (8.7%) had a previous history of coronary heart disease, 14 (1.5%) had peripheral artery disease (PAD), and 10 (1.09%) had aortic aneurysm. Sex-specific quartiles of uric acid were calculated. The fourth quartile of uric acid was associated with higher TGs, MBPS, mean SBP, daytime SBP, daytime DBP, nighttime SBP, nighttime DBP, office SBP, office DBP, higher creatinine, glucose, and white blood cell count, but lower percentage of nighttime fall in SBP and DBP (Table I). Patients in quartile 4 were also older than those in the first and second quartiles of uric acid. Those in quartile 4 had a higher percentage of diabetes and MACEs than the other quartiles (Table II). Overall, mean MBPS was 37.4±9.2 mm Hg and mean uric acid was 5.6±1.0. MBPS was significantly lower in patients in the first quartile of uric acid compared with those in the second quartile (*P*=.0007), third quartile (*P*<.0001), and fourth quartile (*P*<.0001). In addition, the values of MBPS were significantly increased in patients across the quartiles of SUA (*P*<.0001).

**TABLE I.** Characteristics of the Study Population According to Sex-Specific Quartiles of Uric Acid

| | Means±SD and *P* Values | | | | |
|---|---|---|---|---|---|
| Variable | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | *P* Value |
| Age, y | 56.9±12.2[a] | 55.4±12.2[a] | 58.7±13.3 | 61.6±12.8 | <.001 |
| HDL cholesterol, mg/dL | 45.9±13.1 | 46.6±12.6 | 45.1±12.1 | 44.0±11.6 | .128 |
| LDL cholesterol, mg/dL | 124.9±28.6 | 121.9±26.3 | 130.2±32.9 | 126.6±33.7 | .028 |
| Triglycerides, mg/dL | 147.0±55.2[a] | 146.6±66.5[a] | 166.4±86.0 | 172.8±75.5 | <.001 |
| Morning BP surge | 33.3±7.1[a] | 36.3±8.7[a] | 40.0±9.6 | 40.9±9.6 | <.001 |
| Systolic BP, mm Hg | 135.6±9.8[a] | 137.3±10.1[a] | 138.7±10.8 | 141.5±11.2 | <.001 |
| Diastolic BP, mm Hg | 88.0±8.1 | 89.2±7.9 | 89.6±9.7 | 89.3±9.5 | .187 |
| Day systolic BP, mm Hg | 138.8±9.8[a] | 140.2±10.2[b] | 142.0±11.0 | 144.3±11.0 | <.001 |
| Day diastolic BP, mm Hg | 90.5±7.9 | 91.4±7.6 | 92.0±8.8 | 91.6±9.0 | .252 |
| Night systolic BP, mm Hg | 124.7±13.1[a] | 127.7±14.1[b] | 128.6±15.0 | 133.2±15.7 | <.001 |
| Night diastolic BP, mm Hg | 78.2±9.1 | 80.8±10.3 | 80.1±11.3 | 81.8±11.3 | .002 |
| Office systolic BP, mm Hg | 159.9±15.8[b] | 161.8±16.4 | 164.4±16.6 | 164.9±17.1 | .004 |
| Office diastolic BP, mm Hg | 101.5±15.6 | 103.0±16.6 | 106.5±17.2 | 106.8±18.2 | .001 |
| Nighttime fall in systolic BP, % | 10.0±7.2[b] | 9.1±7.5 | 9.2±7.7[c] | 7.3±9.0 | .003 |
| Nighttime fall in diastolic BP, % | 13.3±8.3[b] | 11.6±8.8 | 12.8±8.8[c] | 10.2±9.3 | .001 |
| Creatinine, mg/dL | 0.9±0.1[a] | 0.9±0.2[a] | 0.9±0.2[b] | 1.0±0.2 | <.001 |
| eGFR, mL/min/1.73 $m^2$ | 94.6±10.8[a] | 94.8±11.3[a] | 91.1±12.3 | 87.5±11.3 | <.001 |
| Glucose, mg/dL | 104.1±31.0[b] | 103.6±19.6[b] | 106.2±22.4 | 112.3±31.1 | .002 |
| White blood cells, $\times 10^3/\mu L$ | 7400±2000 | 7200±1700[c] | 7600±1600 | 7700±1800 | .016 |

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PAD, peripheral artery disease. [a]*P*<.001 compared with quartile 4. [b]*P*<.01 compared with quartile 4. [c]*P*<.05 compared with quartile 4.

### Major Adverse Cardiac Events

In unadjusted Cox regression both MBPS (HR, 1.059; 95% CI, 1.035–1.083; *P*<.0001) and uric acid (HR, 1.724; 95% CI, 1.443–2.06; *P*<.0001) were associated with an increased hazard of MACEs. In Cox regression, uric acid as a continuous variable was associated with an increased hazard of a MACE (HR, 1.425) after adjusting for age, sex, diabetes, hypertension status, smoking status, history of aortic aneurysm, coronary heart disease or PAD, TGs, MBPS, and mean SBP (Table III). In Cox regression, the fourth quartile of sex-specific quartiles of uric acid was associated with an increased hazard of a major cardiac event (HR, 2.934) after adjusting for age, sex, diabetes, hypertension status, smoking status, history of aortic aneurysm, coronary heart disease or PAD, TGs, MBPS, and mean SBP (Table IV). In addition, uric acid was still significant after further adjusting for eGFR measured by the the CKD-EPI equation (Table V and Table VI).

## DISCUSSION

In the current study, we tested the hypothesis that MBPS and elevated SUA levels are related with each other and with MACE in a large cohort of hypertensive patients without CKD. Our primary findings were that: (1) both MBPS and SUA level were associated with MACE, (2) SUA level and MBPS were associated with each other, and (3) patients in the highest quartile stratified by elevated MBPS and SUA level had a 3.55 odds of MACE compared with those in the lowest quartile. To the best of our knowledge, the last finding is novel and has not been demonstrated before.

**TABLE II.** Characteristics of the Study Population According to Quartiles of Serum Uric Acid

| Variable | Quartile 1 (n=239) (%) | Quartile 2 (n=259) (%) | Quartile 3 (n=213) (%) | Quartile 4 (n=210) (%) | *P* Value |
|---|---|---|---|---|---|
| Female sex | 110 (46.0) | 118 (45.6) | 95 (44.6) | 97 (46.2) | .987 |
| Diabetes | 26 (10.9) | 45 (17.4) | 35 (16.4) | 54 (25.7) | .001 |
| Smoking | 48 (20.1) | 54 (20.9) | 53 (24.9) | 49 (23.3) | .585 |
| Hypertension | 92 (38.5) | 97 (37.5) | 94 (44.1) | 89 (42.4) | .412 |
| Coronary artery disease | 19 (8.0) | 24 (9.3) | 17 (8.0) | 20 (9.5) | .375 |
| PAD | 5 (2.1) | 5 (1.9) | 3 (1.4) | 1 (0.5) | |
| Aortic aneurysm | 2 (0.8) | 0 (0) | 3 (1.4) | 5 (2.4) | |
| MACE | 9 (3.8) | 8 (3.1) | 36 (16.9) | 50 (23.8) | <.0001 |

Abbreviations: MACE, major adverse cardiac event; PAD, peripheral artery disease.

**TABLE III.** Cox Regression of Major Adverse Cardiac Events on Uric Acid as a Continuous Variable

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Age, y | 1.06 (1.04–1.08) | <.0001 |
| Female sex | 1.34 (0.89–2.02) | .160 |
| Diabetes | 2.85 (1.87–4.35) | <.0001 |
| Hypertension | 0.74 (0.48–1.13) | .167 |
| Smoking | 1.47 (0.94–2.32) | .095 |
| Previous aortic aneurysm | 2.77 (1.22–6.28) | .015 |
| Previous coronary artery disease | 2.00 (1.09–3.66) | .023 |
| PAD | 1.47 (0.19–11.51) | .708 |
| HDL cholesterol, mg/dL | 0.98 (0.96–0.99) | .014 |
| LDL cholesterol, mg/dL | 1.01 (1.00–1.01) | .006 |
| Triglycerides, mg/dL | 0.99 (0.99–1.00) | .445 |
| MBPS | 1.06 (1.04–1.08) | <.0001 |
| Systolic BP, mm Hg | 1.02 (1.00–1.04) | .047 |
| Uric acid | 1.43 (1.18–1.72) | .0002 |

Abbreviations: BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein cholesterol; HR, hazard ratio; LDL, low-density lipoprotein cholesterol; MBPS, morning blood pressure surge; PAD, peripheral artery disease.

**TABLE IV.** Cox Regression of Major Adverse Cardiac Events on Uric Acid as a Categorical Variable

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Age, y | 1.06 (1.04–1.08) | <.0001 |
| Female sex | 1.23 (0.82–1.84) | .324 |
| Diabetes | 2.88 (1.86–4.39) | <.0001 |
| Hypertension | 0.70 (0.45–1.08) | .102 |
| Smoking | 1.48 (0.94–2.34) | .089 |
| Previous aortic aneurysm | 2.76 (1.21–6.28) | .015 |
| Previous coronary artery disease | 2.08 (1.14–3.78) | .016 |
| PAD | 1.17 (0.15–9.38) | .882 |
| HDL, mg/dL | 0.98 (0.96–0.99) | .020 |
| LDL, mg/dL | 1.01 (1.00–1.01) | .009 |
| Triglycerides, mg/dL | 0.99 (0.99–1.00) | .399 |
| MBPS | 1.05 (1.03–1.08) | <.0001 |
| Systolic BP, mm Hg | 1.02 (1.00–1.04) | .054 |
| Quartile 2 vs quartile 1 | 0.68 (0.26–1.80) | .438 |
| Quartile 3 vs quartile 1 | 2.09 (0.96–4.58) | .063 |
| Quartile 4 vs quartile 1 | 2.93 (1.38–6.24) | .005 |

Abbreviations: BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein cholesterol; HR, hazard ratio; LDL, low-density lipoprotein cholesterol; MBPS, morning blood pressure surge; PAD, peripheral artery disease.

Previous studies have reported conflicting results regarding the relationship between MBPS and cardiovascular outcomes. While some studies have shown a positive association,[24,26] others described a negative association.[11,27] In this study, we evaluated the relationship of morning uric acid levels with early MBPS and demonstrated that SUA level and MBPS were correlated with each other. In this regard, Kario and colleagues[24] previously reported that patients in the highest quartile of SUA levels had higher MBPS. Another study demonstrated that MBPS and SUA level are correlated,[28] but there was no risk stratification with special respect to cardiovascular outcomes. Although no cause and effect relationship can be suggested due to the observational design of our study, we hypothesize that SUA level may play a direct role in the elevation of MBPS.

**TABLE V.** Cox Regression of Major Adverse Cardiac Events on Uric Acid as a Continuous Variable With eGFR

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Age, y | 1.04 (1.01–1.07) | .004 |
| Female sex | 1.26 (0.83–1.91) | .277 |
| Diabetes | 2.74 (1.78–4.21) | <.0001 |
| Hypertension | 0.78 (0.51–1.19) | .258 |
| Smoking | 1.44 (0.91–2.28) | .115 |
| Previous aortic aneurysm | 2.83 (1.23–6.47) | .014 |
| Previous coronary artery disease | 2.08 (1.14–3.78) | .017 |
| PAD | 1.38 (0.17–10.82) | .754 |
| HDL cholesterol, mg/dL | 0.97 (0.96–0.99) | .020 |
| LDL cholesterol, mg/dL | 1.01 (1.01–1.01) | .007 |
| Triglycerides, mg/dL | 0.99 (0.99–1.01) | .399 |
| MBPS | 1.06 (1.04–1.08) | <.0001 |
| Systolic BP, mm Hg | 1.02 (0.99–1.04) | .072 |
| eGFR, mL/min/1.73 $m^2$ | 0.97 (0.95–1.01) | .132 |
| Uric acid | 1.38 (1.15–1.67) | .0006 |

Abbreviations: BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MBPS, morning blood pressure surge; PAD, peripheral artery disease.

Why would an elevated SUA level be related to an increase in MBPS? One mechanism could be related to the known opposing effects of uric acid and nitric oxide (NO) in the circadian rhythm.[29] During early morning hours, serum NO falls while uric acid rises. While not directly tested in this study, hyperuricemia is strongly associated with endothelial dysfunction and uric acid has been shown to reduce endothelial NO bioavailability via multiple mechanisms, including direct scavenging, induction of oxidants, or altering arginine transport or metabolism.[18,30–33] Lowering uric acid has also been reported to improve endothelial function in humans.[20,21] Thus, a role of uric acid on NO and circadian rhythm is possible.

Other mechanisms may also be operative, including potential activation of the renin-angiotensin system[34] or induction of oxidative stress,[17] both of which are associated with MBPS.[35,36] Plasma renin activity, angiotensin II, and aldosterone levels are all increased before awakening and then further increase after awakening.[9,37] One of the important aspects of the MBPS is the dependency of measurements on dipping/nondipping status,[11,38] although, at least in some

**TABLE VI.** Cox Regression of Major Adverse Cardiac Events on Uric Acid as a Categorical Variable With eGFR

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Age, y | 1.04 (1.01–1.07) | .006 |
| Female sex | 1.16 (0.77–1.76) | .471 |
| Diabetes | 2.76 (1.80–4.24) | <.0001 |
| Hypertension | 0.74 (0.48–1.14) | .171 |
| Smoking | 1.45 (0.92–2.29) | .114 |
| Previous aortic aneurysm | 2.83 (1.23–6.51) | .014 |
| Previous coronary artery disease | 2.15 (1.18–3.90) | .012 |
| PAD | 1.14 (0.14–9.14) | .901 |
| HDL cholesterol, mg/dL | 0.97 (0.96–0.99) | .029 |
| LDL cholesterol, mg/dL | 1.01 (1.02–1.01) | .011 |
| Triglycerides, mg/dL | 0.99 (0.99–1.02) | .361 |
| MBPS | 1.05 (1.03–1.07) | <.0001 |
| Systolic BP, mm Hg | 1.02 (0.99–1.04) | .082 |
| eGFR, mL/min/1.73 $m^2$ | 0.97 (0.95–1.01) | .142 |
| Quartile 2 vs quartile 1 | 0.67 (0.26–1.78) | .430 |
| Quartile 3 vs quartile 1 | 1.96 (0.89–4.32) | .092 |
| Quartile 4 vs quartile 1 | 2.75 (1.29–5.88) | .008 |

Abbreviations: BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MBPS, morning blood pressure surge; PAD, peripheral artery disease.

studies, the association between MBPS and outcomes is independent of dipping and nondipping status.[24]

## STUDY LIMITATIONS

Our study has some limitations. Firstly, the cross-sectional design precludes us to conclude cause and effect relationships. Secondly, the measurements were performed once and the reproducibility of MBPS is questionable in some studies.[39,40] Thirdly, we relied on diaries, and actual sleeping and waking periods were not measured by more objective measures such as actigraphy. Fourthly, physical activity of the patients was not assessed. Lastly, the mean of MBPS was relatively high in our study. Although we don't now the exact causes of this, it may be caused by a high number of women with diabetes in our cohort.

## CONCLUSIONS

We demonstrated for the first time that patients stratified for both elevated SUA level and MBPS have increased MACEs compared with other patients. Studies are needed to determine whether specific medications that decrease uric acid will translate into lower MBPS and improved cardiovascular outcomes.

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*Conflict of Interest: Dr Johnson is listed as an inventor on a patent for allopurinol to treat essential hypertension and is also an inventor on patent applications related to lowering uric acid in the prevention or treatment of hypertension, insulin resistance, and diabetic nephropathy. He also serves on the scientific board of Amway. All other authors declared no competing interests and had access to the data and played a role in writing this manuscript.*

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