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ORIGINAL ARTICLE

Morning blood pressure surge is associated with serum gamma-glutamyltransferase activity in essential hypertensive patients

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The phenomenon that blood pressure rises sharply in the morning is called 'Morning Blood Pressure Surge' (MBPS). Serum gamma-glutamyltransferase (GGT) is a proinflammatory marker involved in the pathogenesis of cardiovascular diseases. Although both are novel cardiovascular risk factors associated with inflammation and atherosclerosis, the specific relationship between MBPS and serum GGT is unknown. This study investigates the relationship between MBPS and serum GGT activity in essential hypertensive patients. Totally, 320 hypertensive patients were recruited. Mean MBPS was 17.0 ± 12.9 mm Hg. MBPS was positively correlated with age ($r = +0.222$, $P < 0.0001$), body mass index ($r = +0.132$, $P = 0.018$), GGT ($r = +0.271$, $P < 0.0001$), daytime augmentation index adjusted for heart rate (AIx@75) ($r = +0.140$, $P = 0.014$), 24-h pulse wave velocity (PWV) ($r = +0.143$, $P = 0.014$) and daytime PWV ($r = +0.158$, $P = 0.007$). From the 25th to 75th quartile of serum GGT, MBPS increased significantly ($P_{trend} < 0.0001$). In multivariate linear regression analysis, MBPS was independently associated with age ($P = 0.002$), dipping status ($P < 0.0001$) and logGGT ($P < 0.0001$). In conclusion, MBPS is independently associated serum GGT activity in essential hypertensive patients. This is the first study in the literature to demonstrate an independent and a dose–response relationship between the two novel cardiovascular risk factors, MBPS and serum GGT, in this patient population.

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INTRODUCTION

The importance of hypertension as a risk factor of target organ damage and cardiovascular disease is widely acknowledged. Although clinic blood pressure (BP) is used as the primary tool for the diagnosis and management of hypertension, out of clinic BP measurements, by the use of ambulatory BP monitoring, is considered more reliable than clinic BP measurements because they are more reproducible.[1]

BP exhibits a diurnal variation, reaching the highest level in the morning and then declining to reach a trough level at night. The phenomenon that BP rises sharply in the morning is called 'Morning Blood Pressure Surge' (MBPS). MBPS has been reported to occur in response to sudden activation of the sympathetic nervous system and increased α-mediated sympathetic activity,[2] and can be measured reliably using ambulatory BP monitoring. MBPS is considered to be a cardiovascular risk factor.[1] The study by Kario *et al.*[3] was the first to show that an excessive MPBS was a predictor of subsequent stroke in elderly hypertensive patients, independent of ambulatory BP levels and target organ damage. Subsequently, in the Ohasama study, an increased risk of cerebral hemorrhage was observed in subjects with a large MBPS (⩾25 mm Hg).[4] Recently, Li *et al.*[5] reported that MBPS exceeding the 90th percentile was a significant and independent predictor of mortality and cardiovascular events.

Serum gamma-glutamyltransferase (GGT), a plasma membrane-bound enzyme, has been used as a biological marker for alcohol intake or liver cell damage.[6] GGT has a pro-oxidative effect, as it is involved in the degradation of the antioxidant glutathione, and has an indirect pro-oxidative effect by causing low-density lipoprotein cholesterol oxidation in the presence of iron. GGT is also considered as a proinflammatory marker, and serum GGT activity found within atherosclerotic lesions directly contributes to atherosclerosis progression.[7] Studies have shown that serum GGT might have a role in the pathogenesis of cardiovascular disease, diabetes mellitus, stroke and metabolic syndrome.[6,7] Shankar *et al.*[8] reported that higher serum GGT levels were positively associated with prehypertension in US adults free of hypertension and cardiovascular disease. Stranges *et al.*[9] showed that serum GGT, within the physiological range, was a strong predictor of incident hypertension in a dose–response relationship. Kawamoto *et al.*[10] reported that both systolic and diastolic BPs increased significantly with increasing GGT levels among community-dwelling men in Japan. Most recently, Chun *et al.*[6] and Kim *et al.*[7] disclosed that serum GGT was independently associated with incident prehypertension and hypertension in Korean adults, respectively.

In this study, we investigated whether MBPS, which is a cardiovascular risk factor, is associated with serum GGT in patients with essential hypertension.

MATERIALS AND METHODS

The study had a single-center, cross-sectional design. Totally, 320 consecutive patients from outpatient clinics with essential hypertension who agreed to participate in this study were recruited. The study protocol complied with the Helsinki Declaration of 1975, as revised in 2000, and was approved by the Institutional Ethics Committee. All participants gave informed consent. The exclusion criteria were the presence of secondary

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hypertension, cardiac arrhythmias, congestive heart failure, inflammatory diseases (acute infection, autoimmune diseases), malignancy, sleep apnea, positive HBsAg and/or positive anti-HCV antibody tests and shift working. None of the patients had alcohol abuse. Patients with known coronary artery disease, who were free from acute coronary syndrome, myocardial infarction, angina pectoris or coronary revascularization procedure within the last 3 months, were included. All patients underwent the following procedures; anamnesis, physical examination, routine biochemical testing, office and ambulatory BP monitoring and calculation of sleep-through MBPS.

Body mass index (BMI) was calculated as (weight (kg))/(height (m))^2. Hypertension was defined as systolic BP (SBP) of 140 mm Hg or more, diastolic BP (DBP) of 90 mm Hg or more or both. The diagnosis of type 2 diabetes mellitus was based on the American Diabetes Association criteria.[11] Coronary artery disease was defined as a history of acute coronary syndrome, myocardial infarction, angina pectoris or coronary revascularization procedure (coronary stent replacement and coronary artery by-pass graft surgery). Cerebrovascular disease was defined as a history of stroke, transient ischemic attack or carotid revascularization procedure. Peripheral arterial disease was defined as a history of intermittent claudication, ischemic leg ulcer, peripheral revascularization or amputation for critical limb ischemia.

Level of kidney function was assessed by estimated glomerular filtration rate (eGFR) calculated by Modification of Diet in Renal Disease formula,[12] as follows;

eGFR (ml min^{-1} per 1.73 m^2) = 186 × serum creatinine (mg dl^{-1})$^{-1.154}$ × age (years)$^{-0.203}$ × (1.210 if African-American) × (0.742 if female).

Office BP measurement

Office BP measurements were recorded by Omron MZ model (Omron Health Care, Mukou City, Kyoto, Japan) sphygmomanometer. BPs were measured according to European Society of Hypertension Guidelines.[13]

Ambulatory BP measurement

Ambulatory BP measurement was performed by the validated Mobil-O-Graph Arteriograph (I.E.M. GmbH, Stolberg, Germany) device based on the method described in elsewhere.[14] All patients were instructed to rest or sleep between 2200 and 0700 hours (nighttime) and to continue their usual activities between 0700 and 2200 hours (daytime). By using Mobil-O-Graph arteriograph device with an ARC solver method (Austrian Institute of Technology, Vienna), pulse wave forms from brachial artery were recorded during 24 h. This new BP monitor oscillometrically captures pulse wave form from brachial artery by an upper-arm cuff and measures pulse wave velocity (PWV). Within a single measurement cycle, cuff pressure is hold for a time period of 10 s at diastolic value during cuff deflation. Recording time of oscillometric signal at diastolic level allows derivation of augmentation index adjusted for heart rate (AIx@75). Measurements were automatically calculated during 24-h, daytime and nighttime.[14,15]

Morning BP was defined as the average of BPs during the first 2 h after wake-up time (four BP readings). The lowest BP was defined as the average BP of three readings centered on the lowest nighttime reading (that is, the lowest reading plus the readings immediately before and after). The sleep-through MBPS was calculated as the morning SBP minus the lowest SBP.[3]

Biochemical analysis

Blood samples were obtained after participants had fasted overnight. Complete blood counts were made by using automated blood counting device. Serum uric acid was determined by enzymatic method. Other biochemical parameters were measured by standard methods.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality of data was evaluated by Kolmogorov–Smirnov test (Lilliefors modification). Data are shown as mean ± s.d. for normally distributed continuous variables, median (range) for non-normally distributed continuous variables, and as a percentage (%), where appropriate. Spearman nonparametric correlation analysis was run between the MBPS and the clinical, laboratory and ambulatory BP parameters and eGFR. Kendall's Tau correlation analysis was used to assess the correlation between MBPS and the dipping status. Scatterplot graphic between MBPS and logGGT was run with Pearson correlation analysis. Comparison of the MBPS among GGT quartiles was carried out by one-way analysis of variance test. For the posthoc comparison, Tukey test was used. Multivariate linear regression analysis was performed with stepwise method to determine the possible factors (including age, gender, BMI, smoking, 24-h SBP, 24-h DBP, dipping status, diabetes mellitus, coronary artery disease, use of acetylsalicylic acid, statin and antihypertensive drugs, uric acid, alanine aminotransferase, logGGT and logeGFR as variables) independently related to MBPS. Because GGT and eGFR were not normally distributed, logarithmic conversion was performed before linear regression analysis. Results were considered statistically significant if two-tailed P is less than 0.05.

RESULTS

Totally, 320 hypertensive patients (male/female: 133/187) were included. Table 1 demonstrates the basal demographic and clinical characteristics of the study population. Overall, 79.7% of the patients were nondippers. The laboratory characteristics and eGFR of the study population are shown in Table 2.

Table 1. The demographic and clinical characteristics of the study population

Parameter	N = *320*
Age (years)	54.4 ± 14.4
Gender (male/female)	133/187
Body mass index (kg m^{-2})	29.1 ± 5.6
Smoking (smoker/nonsmoker)	92/228
Diabetes mellitus (present/absent; *n*)	125/195
Coronary artery disease (present/absent; *n*)	107/213
Cerebrovascular disease (present/absent; *n*)	11/309
Peripheral arterial disease (present/absent; *n*)	5/315
Statin, *n* (%)	58 (18.1)
Acetylsalicylic acid, *n* (%)	96 (30.0)
ACEI, *n* (%)	67 (20.9)
ARB, *n* (%)	106 (33.1)
Calcium channel blocker, *n* (%)	124 (38.8)
α-Blocker, *n* (%)	60 (18.8)
β-Blocker, *n* (%)	72 (22.5)
Thiazide diuretics, *n* (%)	57 (17.8)
Loop diuretic, *n* (%)	17 (5.3)
Dippers/nondippers, *n* (%)	65 (20.3)/255 (79.7)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. The laboratory characteristics and eGFR of the study population

Parameter	N = *320*
Hemoglobin (g l^{-1})	134.3 ± 19.2
Hematocrit (%)	40.3 ± 5.2
Albumin (g l^{-1})	40.7 ± 4.9
Urea (mmol l^{-1})	14.4 ± 8.9
Creatinine (μmol l^{-1})	70.7 (44.2–468.5)
Sodium (mmol l^{-1})	138.4 ± 3.1
Potassium (mmol l^{-1})	4.4 ± 0.4
Calcium (mmol l^{-1})	2.4 ± 1.4
Phosphorus (mmol l^{-1})	1.1 ± 0.2
Total cholesterol (mmol l^{-1})	4.9 ± 1.1
HDL-C (mmol l^{-1})	1.1 ± 0.3
LDL-C (mmol l^{-1})	3.1 ± 0.9
Triglyceride (mmol l^{-1})	1.7 ± 0.9
Gamma-glutamyltransferase (U l^{-1})	21.0 (7.0–382.0)
Alanine aminotransferase (U l^{-1})	21.4 ± 12.6
Uric acid (μmol l^{-1})	333.7 ± 115.6
eGFR (ml min^{-1} per 1.73 m^2)	80.8 (11.8–158.7)

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3. The office and ambulatory blood pressure parameters, PWV and AIx@75 of the study population

Parameter	N = *320*
Office SBP (mm Hg)	133.5 ± 18.5
Office DBP (mm Hg)	84.6 ± 11.4
24-h SBP (mm Hg)	125.7 ± 17.4
Daytime SBP (mm Hg)	127.1 ± 17.2
Nighttime SBP (mm Hg)	121.4 ± 19.5
24-h DBP (mm Hg)	79.1 ± 11.7
Daytime DBP (mm Hg)	80.7 ± 11.6
Nighttime DBP (mm Hg)	74.4 ± 12.9
24-h MAP (mm Hg)	100.4 ± 13.3
Daytime MAP (mm Hg)	101.9 ± 13.3
Nighttime MAP (mm Hg)	95.8 ± 15.1
24-h pulse pressure (mm Hg)	46.6 ± 11.3
Daytime pulse pressure (mm Hg)	46.4 ± 11.3
Nighttime pulse pressure (mm Hg)	47.0 ± 12.4
24-h heart rate (mm Hg)	75.6 ± 10.9
Daytime heart rate (mm Hg)	78.1 ± 11.5
Nighttime heart rate (mm Hg)	68.4 ± 10.6
Maximum daytime SBP (mm Hg)	157.8 ± 26.2
Maximum nighttime SBP (mm Hg)	141.0 ± 25.1
Maximum daytime DBP (mm Hg)	102.2 ± 15.1
Maximum nighttime DBP (mm Hg)	89.2 ± 14.8
Minimum daytime SBP (mm Hg)	99.5 ± 16.4
Minimum nighttime SBP (mm Hg)	104.5 ± 18.7
Minimum daytime DBP (mm Hg)	57.1 ± 12.4
Minimum nighttime DBP (mm Hg)	59.7 ± 12.9
MBPS (mm Hg)	17.0 ± 12.9
24-h AIx@75 (%)	23.1 ± 9.9
Daytime AIx@75 (%)	23.1 ± 9.6
Nighttime AIx@75 (%)	22.9 ± 12.4
24-h PWV (m s^{-1})	7.5 ± 1.9
Daytime PWV (m s^{-1})	7.5 ± 1.9
Nighttime PWV (m s^{-1})	7.4 ± 1.9

Abbreviations: AIx@75, augmentation index adjusted for heart rate; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; MBPS, morning blood pressure surge; PWV, pulse wave velocity; SBP, systolic blood pressure.

The median eGFR was 80.8 ml min^{-1} per 1.73 m^2. Table 3 demonstrates the office and ambulatory BP parameters, PWV and AIx@75 of the study population. The mean MBPS was 17.0 ± 12.9 mm Hg.

The correlation analysis revealed that MBPS was positively correlated with age (*r*: +0.222, $P < 0.0001$), BMI (*r*: +0.132, *P*: 0.018), GGT (*r*: +0.271, $P < 0.0001$), daytime AIx@75 (*r*: +0.140, *P*: 0.014), 24-hour PWV (*r*: +0.143, *P*: 0.014) and daytime PWV (*r*: +0.158, *P*: 0.007). The MBPS was positively correlated with logGGT (*r*: +0.293, $P < 0.0001$) (Figure 1). In Kendall's Tau correlation analysis, MBPS was correlated with the dipping status (*r*: −0.216, $P < 0.0001$). The other parameters were not correlated with MBPS (Table 4). From the 25th to 75th quartile of serum GGT, MBPS increased significantly ($P_{trend} < 0.0001$) (Figure 2). Post hoc analysis showed that MBPS was significantly different between <25th and >75th quartiles ($P < 0.0001$), 25th-50th and >75th quartiles (*P*: 0.001) and 50th–75th and >75th quartiles (*P*: 0.048).

Multivariate linear regression analysis for factors that might be associated with MBPS (the model included age, gender, BMI, smoking, 24-h SBP, 24-h DBP, dipping status, diabetes mellitus, coronary artery disease, use of acetylsalicylic acid, statin and antihypertensive drugs, uric acid, alanine aminotransferase, logGGT and logeGFR as independent variables) demonstrated that MBPS was independently associated with age (*P*: 0.023), dipping status ($P < 0.0001$) and logGGT ($P < 0.0001$) (Table 5).

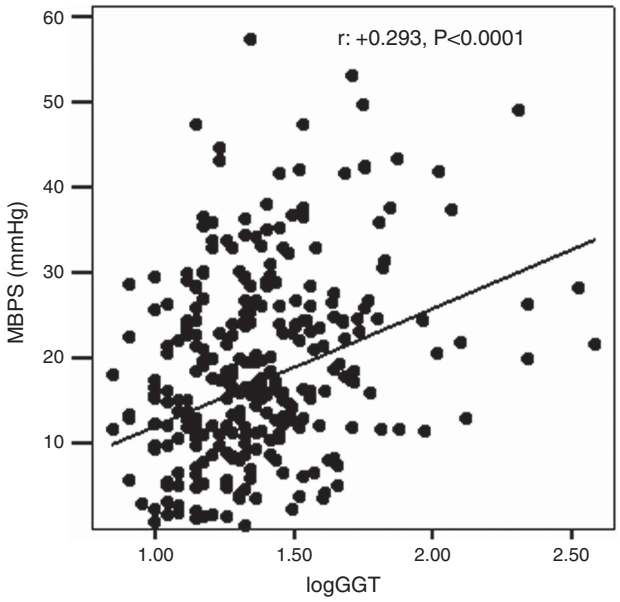

Figure 1. The scatterplot graphic between morning BP surge and logarithmically converted GGT. logGGT, logarithmically transformed GGT.

Table 4. The correlation of morning blood pressure surge with clinical, laboratory and ambulatory blood pressure parameters and estimated glomerular filtration rate of the study population

Correlation coefficient (r)	*MBPS* (r)	P-*value*
Age (years)	+0.222	< 0.0001
Body mass index (kg m^{-2})	+0.132	0.018
Hemoglobin (g l^{-1})	+0.084	0.135
Hematocrit (%)	+0.090	0.108
Albumin (g l^{-1})	+0.020	0.732
Urea (mmol l^{-1})	+0.067	0.242
Creatinine (μmol l^{-1})	+0.004	0.942
Sodium (mmol l^{-1})	−0.016	0.777
Potassium (mmol l^{-1})	+0.012	0.829
Calcium (mmol l^{-1})	−0.034	0.558
Phosphorus (mmol l^{-1})	−0.040	0.510
Total cholesterol (mmol l^{-1})	+0.001	0.995
HDL-C (mmol l^{-1})	−0.027	0.645
LDL-C (mmol l^{-1})	+0.022	0.706
Triglyceride (mmol l^{-1})	+0.073	0.204
Gamma-glutamyltransferase (U l^{-1})	+0.271	< 0.0001
Alanine aminotransferase (U l^{-1})	+0.142	0.012
Uric acid (μmol l^{-1})	+0.075	0.214
24-h AIx@75 (%)	+0.111	0.051
Daytime AIx@75 (%)	+0.140	0.014
Nighttime AIx@75 (%)	−0.010	0.864
24-h PWV (m s^{-1})	+0.143	0.014
Daytime PWV (m s^{-1})	+0.158	0.007
Nighttime PWV (m s^{-1})	+0.101	0.084
eGFR (ml min^{-1}per 1.73 m^2)	+0.013	0.819

Abbreviations: AIx@75, augmentation index adjusted for heart rate; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MBPS, morning blood pressure surge; PWV, pulse wave velocity.

DISCUSSION

Our results showed that MBPS was positively correlated with age, BMI, serum GGT, daytime AIx@75, 24-h PWV and daytime PWV in hypertensive individuals. From the 25th to 75th quartile of serum

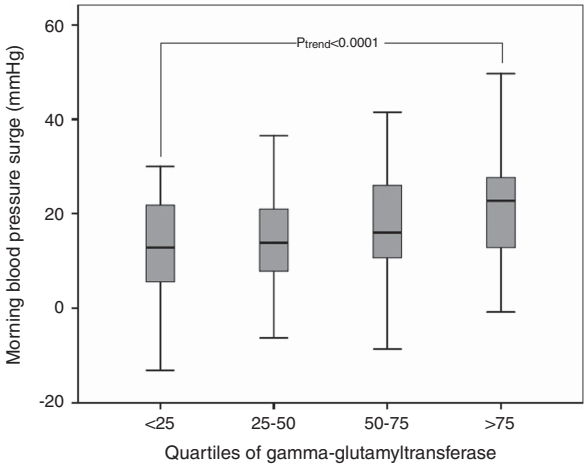

Figure 2. The distribution of morning BP surge according to quartiles of GGT.

Table 5. Multivariate linear regression analysis of factors associated with morning blood pressure surge in the study population

Parameter	β	*95% confidence interval*	P-*value**
Age	0.156	0.056 to 0.257	0.002
Dipping status	−8.595	−12.289 to −4.901	< 0.0001
logGGT	10.749	5.435 to 16.063	< 0.0001

Abbreviations: GGT, gamma-glutamyltransferase; logGGT; logaritmic-transformed GGT. *Adjusted for gender, body mass index, smoking, 24-h systolic blood pressure, 24-h diastolic blood pressure, diabetes mellitus, coronary artery disease, use of acetylsalicylic acid, statin and antihypertensive drugs, uric acid, alanine aminotransferase and logaritmic-transformed estimated glomerular filtration rate.

GGT, MBPS increased significantly. In adjusted analysis, MBPS was independently associated only with age, dipping status and logGGT. This is the first study in the literature to demonstrate an independent association between MBPS and serum GGT, which is a proinflammatory marker, in patients with essential hypertension.

BP fluctuates in a daily pattern of peaks and troughs known as the 'Circadian Rhythm'.[16] In the early morning, an abrupt and steep acceleration in BP occurs, coincident with arousal and rising from overnight sleep. A slow but steady increase in BP is then observed over the early morning hours.[17] This is known as the 'Morning Blood Pressure Surge', and is thought to result from increased physical activity and endogenous factors, such as sympathetic nervous system and renin–angiotensin–aldosterone system activities, and endothelial function.[16–18] Nitric oxide production rises during morning hours in normotensives, a rise that can be disrupted in patients with hypertension, further potentiating vasoconstriction.[17] MBPS, which is determined by a sum of physiologic and unphysiologic factors, is associated with increased cardiovascular risk.[19] MBPS contributes to target organ damage [2] and is positively correlated with left ventricular mass and increased carotid intima–media thickness.[20] The landmark study by Kario *et al.*[3] showed an association between the MBPS and cardiovascular risk. The authors reported that the top MBPS decile had a threefold greater risk of multiple infarcts or stroke after adjustment for 24-h BP and dipping status.

Lee *et al.*[21] reported that in never-treated essential hypertensive patients, with no other cardiovascular risk factors, age was an independent risk factor for MBPS.[21] Neutel *et al.*[16] found that increasing age was associated with a higher SBP MBPS. However, in the multivariate analysis, age was not significantly associated with MBPS and the authors suggested that the age effect is fully accounted for by changes in other variables, such as BP variability in elderly patients. On the other hand, Sun *et al.*[22] reported that in hypertensive individuals, MBPS was correlated with age. Similarly, we found that MBPS was positively correlated with age in hypertensive individuals, and the association remained significant even after adjusting for potential confounders.

Lee *et al.*[21] disclosed a weak and not statistically significant association between MBPS and BMI in never-treated hypertensive patients. In the study by Neutel *et al.*,[16] MBPS was not affected by BMI in hypertensive patients. In the present study, although we showed a positive correlation between MBPS and BMI, the association lost significance in adjusted analysis.

Cross-sectional studies have indicated that MBPS is associated with vascular remodeling such as atherosclerosis, arterial stiffening and small vessel disease. Inflammation also has an important role in the pathogenesis of atherosclerosis. Studies have reported that inflammatory status is associated with MBPS and MBPS-related atherosclerotic lesions.[23] GGT is an enzyme expressed in serum and most cell surfaces. Emerging evidence has shown that serum GGT might be an important enzyme in the pathogenesis of cardiovascular diseases and GGT has been suggested as a novel biomarker of cardiovascular risk.[6,24] The role of GGT in cardiovascular disease is partly explained by its correlation with conventional cardiovascular risk factors such as dyslipidaemia, hypertension, diabetes mellitus and metabolic syndrome, irrespective of alcohol consumption. However, the exact mechanism linking GGT and cardiovascular disease is still unclear.[25] GGT has a direct role in the generation of reactive oxygen species in the presence of iron or other transition metals, including lipid peroxidation in human biological membranes and is an indirect marker of antioxidant systems, with the primary function of maintaining the intracellular concentration of glutathione in response to oxidative stress.[10] GGT has also been used as a proinflammatory marker because of its indirect involvement in the generation of cysteinyl-glycine, which results in low-density lipoprotein oxidation. The enzyme activity of serum GGT found within atherosclerotic lesions directly contributes to atherosclerosis progression.[7] The current evidence suggests that MBPS and serum GGT are the two novel cardiovascular risk factors associated with inflammation and atherosclerosis. However, the specific relationship between MBPS and serum GGT activity is a matter of interest.

Recent studies disclosed that serum GGT activity is related with BP changes. Chun *et al.*[6] reported that serum GGT was positively associated with the incident prehypertension in healthy Korean men. Karakurt *et al.*[26] found that serum GGT level was higher in patients with prehypertension group than in the control group in Turkish men and women. Stranges *et al.*[9] showed that serum GGT was a significant predictor of incident hypertension among overweight persons with increased central fat distribution. Kotani *et al.*[27] disclosed that the degree of increase in SBP (and DBP only in non-diabetic subjects) was significantly, independently and positively correlated to that of GGT in both diabetic and non-diabetic subjects. In this study, we specifically investigated the relationship between MBPS and serum GGT in patients with essential hypertension. We firstly demonstrated that MBPS was positively correlated with serum GGT (in a dose–response relationship), which remained significant in adjusted analysis along with age and dipping status. The mechanisms underlying the relationship between serum GGT and BP changes are not fully understood. First, serum GGT has been interpreted as a reliable marker of oxidative stress, which increases BP by direct vasoconstriction and sodium retention in the vascular smooth muscle and endothelial cells. Second, insulin resistance could have a role in the association between serum GGT and BP changes, because GGT might be interpreted as a marker for hepatic steatosis and hepatic insulin resistance.[6] Nonetheless, this issue warrants further prospective and interventional studies.

Increasing arterial stiffness is closely associated with atherosclerotic cardiovascular disease.[28] Because pulse wave travels faster in arteries with decreased elasticity, arterial stiffness could be measured by PWV.[2] Augmentation index (AIx) is a composite index that integrates the amount of wave that is reflected back to aorta and the velocity of incident and reflected wave.[29] Aortic PWV and AIx are indices of arterial stiffness and are predictors for cardiovascular diseases.[30] There is a paucity of studies investigating the relationship between arterial stiffness and MBPS. Suh *et al.*[2] studied the association of MBPS with PWV in healthy Korean women. They showed that although arterial stiffness did not show significant association with MBPS, it was associated with higher morning BP. However, their participants were nonhypertensive and they used maximum morning BP_{power} for evaluation of MBPS. Contrarily, Polonia *et al.*[31] reported that MBPS was correlated significantly with PWV. In our study, we showed that MBPS was positively correlated with daytime AIx@75, 24-h PWV and daytime PWV in hypertensive individuals.

This study has limitations that deserve mention. First, our study had a cross-sectional design, which precludes deriving a cause–effect relationship between MBPS and serum GGT activity. Second, although patients were instructed to rest or sleep between predefined hours, the precise sleeping patterns of the patients are unknown. Third, we excluded patients with known viral hepatitis, but as we did not perform routine hepatic ultrasonography, we cannot completely rule out parenchymal liver diseases (fatty liver, cirrhosis, hepatocellular carcinoma and so on). Fourth, different kidney function levels may influence the relationship between MBPS and GGT. However, in the current study, we had limited number of patients with loss of renal function; only 78 patients had eGFR $\leqslant 60\ ml\ min^{-1}$ per $1.73\ m^2$, which precluded us performing subgroup analysis according to stages of chronic kidney disease due to low statistical power. This issue merits further investigation. Lastly, as being hypertensive, our patients were on antihypertensive treatment and this may have been disadvantageous during MBPS assessment. Lastly, we relied on a single serum GGT measurement. However, on the other hand, our patient population is composed of patients with somewhat high cardiovascular risk. Therefore, our findings deserve critical attention.

In conclusion, MBPS is independently associated serum GGT activity in essential hypertensive patients. This is the first study in the literature to demonstrate an independent and a dose–response relationship between the two novel cardiovascular risk factors, MBPS and serum GGT, in this patient population.

What is known about topic

- Morning blood pressure surge is a novel cardiovascular risk factor.
- Gamma-glutamyltransferase is an enzyme involved in the pathogenesis of cardiovascular diseases and a novel biomarker of cardiovascular risk.

What this study adds

- Morning blood pressure surge is independently associated with serum gamma-glutamyltransferase activity in essential hypertensive patients.
- The interplay between morning blood pressure surge and serum gamma-glutamyltransferase activity complies with a dose–response relationship.
- This is the first study in the literature to demonstrate an independent association between morning blood pressure surge and serum gamma-glutamyltransferase activity, which is a proinflammatory marker, in patients with essential hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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