

Correlation of Blood Pressure Circadian Rhythm with Plasma ox-LDL/\$2GPI Complex and Carotid Atherosclerosis in Patients with Essential Hypertension: Postprint

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Abstract

Background Poor control of blood pressure levels in patients with essential hypertension can lead to cardiovascular complications and target organ damage. Currently, there is limited intervention on blood pressure circadian rhythm in clinical practice in China, and effective serological indicators for assessing cardiovascular disease risk in hypertensive patients are lacking. **Objective** To investigate the correlation between abnormal blood pressure circadian rhythm and plasma oxidized low-density lipoprotein (ox-LDL)/\$2-glycoprotein I (2GPI) complex levels, high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and carotid atherosclerosis in patients with essential hypertension. **Methods** A total of 204 patients with essential hypertension were included in the study. All patients underwent 24-hour ambulatory blood pressure monitoring and were divided into three groups based on nocturnal blood pressure reduction: dipper group (83 cases), non-dipper group (83 cases), and reverse dipper group (42 cases). General data of enrolled patients included age, sex, duration of hypertension, hs-CRP, ox-LDL/2GPI complex, and other indicators. Carotid ultrasound examination was also conducted to assess the degree of carotid atherosclerosis. **Results** Multivariate Logistic regression analysis showed that the dipper group had significantly lower levels of ox-LDL/2GPI complex, hs-CRP, IL-6, and degree of carotid atherosclerosis compared to the non-dipper group ($P < 0.05$). Patients in the non-dipper and reverse dipper groups had higher levels of hs-CRP, IL-6, ox-LDL/2GPI complex, and higher proportion of carotid plaques than those in the dipper group. Patients in the reverse dipper group had higher hs-CRP levels than those in the non-dipper group ($P < 0.05$).

Essential hypertension **Circadian rhythm** **High-sensitivity C-reactive protein** **Oxidized low-density lipoprotein/\$2-glycoprotein I complex** **Carotid atherosclerotic disease** **Correlation study**

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Full Text

Correlation Analysis of the Circadian Rhythmicity of Blood Pressure with Ox-LDL/\$2GPI Complex and Carotid Atherosclerosis in Patients with Essential Hypertension

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Abstract

Background: Poor control of blood pressure in patients with essential hypertension can lead to cardiovascular complications and end-organ damage. Currently, there are few interventions targeting the circadian rhythmicity of blood pressure in clinical practice, and effective serologic indicators for assessing cardiovascular disease risk in hypertensive patients are lacking.

Objective: To investigate the correlation between abnormal circadian blood pressure rhythm and plasma levels of oxidized low-density lipoprotein (ox-LDL)/\$2-glycoproteinI (\$2GPI) complex, high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and carotid atherosclerosis in patients with essential hypertension.

Methods: A total of 208 patients with essential hypertension who visited the Department of Cardiovascular Medicine and Hypertension Clinic at the Second Affiliated Hospital of Zhengzhou University between January and June 2024 were enrolled. All participants underwent 24-hour ambulatory blood pressure monitoring and were divided into three groups based on

nocturnal blood pressure decline rate: dipper (83 cases), non-dipper (83 cases), and anti-dipper (42 cases). General patient data were collected, and laboratory tests were performed for blood glucose, renal function, liver function, lipids, thyroid function, electrolytes, IL-6, hs-CRP, and ox-LDL/\$ 2GPI complex. Carotid ultrasound examinations were also conducted. Statistical analysis was performed on LDL/\$ 2GPI complex levels, hs-CRP, IL-6, and carotid atherosclerosis severity. Multivariate logistic regression analysis was used to identify factors influencing carotid plaque formation.

Results: There were no statistically significant differences in gender, age, BMI, smoking status, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or glycated hemoglobin among the three groups ($P > 0.05$). Compared with the dipper group, the non-dipper and anti-dipper groups exhibited significantly higher levels of hs-CRP, IL-6, ox-LDL/\$ 2GPI complex, and a higher prevalence of carotid artery plaques. The anti-dipper group also showed higher hs-CRP level than the non-dipper group ($P < 0.05$). Pearson correlation analysis revealed positive correlations between hs-CRP, IL-6, ox-LDL/\$ 2GPI complex and nighttime systolic blood pressure (nSBP) ($r = 0.424, 0.245, 0.480$ respectively; $P < 0.05$). Multivariate logistic regression analysis identified nSBP (OR = 1.091, 95% CI = 1.023-1.044) as independent risk factors for carotid plaque formation in essential hypertension patients ($P < 0.05$).

Conclusion: Essential hypertension patients with abnormal circadian blood pressure rhythm exhibit higher inflammatory factor levels, more severe carotid atherosclerosis, and elevated plasma ox-LDL/\$ 2GPI complex levels. Plasma ox-LDL/\$ 2GPI complex shows promise as a predictive marker for cardiovascular disease risk in essential hypertension patients.

Keywords: Essential hypertension; Circadian rhythm; High-sensitivity C-reactive protein; Oxidized low-density lipoprotein/\$ 2-glycoprotein I complex; Carotid atherosclerotic diseases; Correlation study

Elevated blood pressure is a major risk factor for cardiovascular and cerebrovascular diseases. Identifying early intervention markers and implementing effective preventive measures to reduce the harm caused by hypertension has become a critical global public health priority. In healthy individuals, blood pressure exhibits dynamic changes with a distinct 24-hour circadian rhythm. Based on the nocturnal blood pressure decline rate, hypertension can be classified into dipper, non-dipper, anti-dipper, and extreme-dipper patterns. Among these, non-dipper and anti-dipper patterns, characterized by inadequate nocturnal blood pressure reduction, are closely associated with target organ damage and increased risk of cardiovascular mortality. Nighttime systolic blood pressure (nSBP) has been identified as the parameter most strongly correlated with cardiovascular disease risk. Sustained elevation of blood pressure may damage vascular endothelium, trigger local inflammatory responses, and alter vascular structure and function,

ultimately leading to atherosclerotic disease. Carotid artery intima-media thickness (cIMT) serves as a marker for early-stage atherosclerosis and can be used to assess systemic vascular disease risk.

Multiple studies have demonstrated that inflammation plays a crucial role in the pathogenesis of target organ damage and cardiovascular disease in hypertension. Inflammatory markers interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) can serve as predictors of cardiovascular events. Oxidized low-density lipoprotein (ox-LDL) can accelerate macrophage lipid uptake, promoting foam cell formation that contributes to atherosclerotic plaque development. Some ox-LDL can form stable ox-LDL/\$\alpha\$2GPI complexes through covalent binding with \$\alpha\$2-glycoprotein I (\$\alpha\$2GPI). These stable complexes have been detected in blood samples from patients with autoimmune disease. These stable complexes may correlate with the severity and adverse outcomes of coronary atherosclerosis. However, the relationship between \$\alpha\$2GPI complex levels as well as carotid atherosclerosis, seeking to identify early serological markers for cardiovascular risk in essential hypertension patients.

1.1 Study Subjects

We enrolled 208 patients with essential hypertension who visited the Hypertension Clinic and Department of Cardiovascular Medicine at the Second Affiliated Hospital of Zhengzhou University between January and June 2024. Inclusion criteria were: (1) age 18-80 years; (2) diagnosis according to the *Chinese Guidelines for the Prevention and Treatment of Hypertension (2018 Revised Edition)*: office blood pressure \$\ge\$140/90 mmHg (1 mmHg=0.133 kPa) on three separate occasions without antihypertensive medication, or ambulatory blood pressure monitoring showing 24-hour average \$\ge\$130/80 mmHg, daytime average \$\ge\$135/85 mmHg, or nighttime average \$\ge\$120/70 mmHg; (3) no antihypertensive medication use or discontinuation for at least 2 weeks. Exclusion criteria included secondary hypertension, diabetes, autoimmune diseases, sleep apnea-hypopnea syndrome, symptomatic heart disease, severe arrhythmia, thyroid dysfunction, severe organ impairment, severe psychiatric or immunodeficiency disorders, malignancy, hematologic disease, acute or chronic infectious diseases, recent major surgery, pregnancy or lactation, and incomplete clinical data. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (approval number: KY2024110), and all participants provided informed consent.

1.2.1 Laboratory Tests

General patient data were collected including gender, age, admission date, height, weight, hypertension history, other medical histories, and smoking/alcohol consumption status. After fasting for at least 8 hours, morning venous blood samples were obtained to measure hs-CRP, IL-6, lipid panel, glycosylated hemoglobin, liver function, renal function, thyroid function, and

electrolytes. Plasma ox-LDL/\$ 2GPI complex levels were measured using an enzyme-linked immunosorbent assay kit (Shanghai Yuanju, YJ790322).

1.2.3 Carotid Ultrasound Examination

Carotid ultrasound examinations were performed using a Hitachi-Aloka Lisendo880 ultrasound system. Bilateral common carotid arteries, carotid bifurcations, and internal/external carotid arteries were scanned to assess vessel walls, luminal diameter, intima-media thickness (IMT), and plaque formation. The far wall of the distal common carotid artery (1.0-1.5 cm below the bifurcation) was selected for measurement perpendicular to the vessel long axis, recording the maximum intima-media thickness. cIMT was measured at end-diastole across three cardiac cycles and averaged. Values of 0.9-1.3 mm were defined as increased cIMT, while ≥ 1.3 mm indicated carotid plaque formation. Patients with normal cIMT were classified as the no-plaque group, while those with increased IMT and/or plaque formation constituted the plaque group.

1.3 Statistical Analysis

SPSS 26.0 software was used for statistical description, comparative analysis, and correlation analysis. Statistical significance was defined as $P < 0.05$. Categorical data were expressed as percentages (%) and compared using the χ^2 test. Normally distributed continuous data were presented as mean \pm standard deviation ($\bar{x} \pm s$) and compared using one-way ANOVA. Non-normally distributed data were expressed as median (P25, P75) and compared using the rank-sum test. Pearson correlation analysis and multivariate logistic regression analysis were performed to explore factors influencing carotid plaque formation in essential hypertension patients.

2.1 Comparison of General Data

There were no statistically significant differences in gender, age, BMI, smoking status, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or glycated hemoglobin among the three groups ($P > 0.05$), as shown in Table 1.

2.2 Comparison of hs-CRP, IL-6, ox-LDL/\$ 2GPI Complex, and Carotid Plaque

Significant differences were observed among the three groups in hs-CRP, IL-6, ox-LDL/\$ 2GPI complex levels, and carotid plaque prevalence ($P < 0.05$). Specifically, the non-dipper and anti-dipper groups exhibited higher hs-CRP, IL-6, and ox-LDL/\$ 2GPI complex levels, along with greater carotid plaque prevalence, compared with the dipper group. The anti-dipper group also showed higher hs-CRP levels than the non-dipper group ($P < 0.05$), as detailed in Table 2.

2.3 Pearson Correlation Analysis of nSBP with hs-CRP, IL-6, and ox-LDL/\$2GPI Complex

Pearson correlation analysis demonstrated positive correlations between nSBP and hs-CRP ($r=0.424$), IL-6 ($r=0.245$), and ox-LDL/\$2GPI complex ($r=0.480$) (all $P<0.05$), as presented in Table 3 .

2.4 Multivariate Logistic Regression Analysis of Factors Affecting Carotid Plaque Formation

Using the presence of carotid plaque as the dependent variable (no=0, yes=1) and statistically significant variables from univariate analysis (nSBP, hs-CRP, IL-6, ox-LDL/\$2GPI complex, all as continuous variables) as independent variables, multivariate logistic regression analysis showed that nSBP (OR=1.091, 95% CI=1.023-1.164), hs-CRP (OR=1.091, 95% CI=1.023-1.164), IL-6 (OR=1.091, 95% CI=1.023-1.164), and ox-LDL/\$2GPI complex (OR=1.033, 95% CI=1.023-1.044) were independent risk factors for carotid plaque formation in essential hypertension patients ($P<0.05$), as shown in Table 4 .

This study investigated the correlation between blood pressure variability and inflammatory markers, plasma ox-LDL/\$2GPI complex levels, and carotid atherosclerosis (identified by yearly markers: non-dipper and anti-dipper) exhibited higher carotid plaque prevalence, elevated inflammatory factors, and increased LDL/\$2GPI complex levels.

Hypertension management receives considerable attention in clinical practice. Compared with office blood pressure, ambulatory blood pressure monitoring (ABPM) provides greater predictive value for cardiovascular and cerebrovascular events and mortality. Traditional clinical practice primarily referenced daytime or morning blood pressure when formulating antihypertensive regimens, overlooking the harm caused by long-term circadian rhythm abnormalities. Recent research has increasingly focused on ABPM results, with clinicians recognizing that circadian rhythm disturbances, particularly persistently elevated nSBP, damage target organs in essential hypertension patients. Consequently, attempts have been made to modify blood pressure rhythms, such as adjusting dosing times (morning versus bedtime), to investigate changes in cardiovascular event rates. A multicenter, controlled, prospective trial of 19,084 hypertensive patients demonstrated that bedtime antihypertensive medication significantly improved nocturnal blood pressure levels and reduced major cardiovascular outcomes (including cardiovascular death, myocardial infarction, coronary revascularization, heart failure, and stroke). However, other studies have found insufficient evidence to determine which dosing time offers superior cardiovascular outcomes or fewer adverse events. Our study indicates that essential hypertension patients with abnormal circadian rhythms exhibit more severe carotid atherosclerosis, and nSBP is an independent risk factor for carotid plaque formation, highlighting the necessity of optimizing antihypertensive regimens to maintain healthy circadian blood pressure patterns.

The relationship between hypertension and inflammation is well-established. Over recent decades, inflammatory markers IL-6 and hs-CRP have been recognized as significantly associated with major cardiovascular composite endpoints,

cardiovascular mortality, and all-cause mortality. These inflammatory factors may be stronger predictors of future cardiovascular events and death than lipid parameters. On one hand, chronic elevation of blood pressure damages vascular endothelium, triggering increased systemic inflammatory responses that affect arterial structure and function. On the other hand, inflammatory responses can cause permanent changes in vascular structure and function, such as irreversible fibrosis and cell death, suggesting a potential bidirectional causal relationship between blood pressure elevation and inflammation. Current anti-inflammatory interventions, such as gene knockout or administration of inflammatory mediator inhibitors, can significantly attenuate hypertension-induced kidney and vascular damage and reduce effects on the central nervous system. Our study, which stratified essential hypertension patients by circadian pattern, demonstrated that patients with circadian rhythm disturbances have higher inflammatory factor levels and more severe carotid plaque, underscoring the importance of controlling inflammation to reduce cardiovascular risk in hypertensive patients and providing guidance for combined antihypertensive and anti-inflammatory therapy to improve prognosis.

ox-LDL is pro-inflammatory and highly immunogenic, promoting atherosclerosis development, though its levels are not easily measured accurately in vivo. Some ox-LDL can form relatively stable ox-LDL/ β 2GPI complexes through covalent binding with endogenous β 2GPI. These complexes can form in arterial intima and be released into circulation, and LDL/ β 2GPI complexes can induce macrophage differentiation into foam cells while activating cellular expression. LDL/ β 2GPI complexes are also considered pro-atherogenic autoantigens, with autoantibodies against these complexes. LDL/ β 2GPI complex levels correlate with more severe carotid atherosclerosis, and that hypertension patients with LDL/ β 2GPI complex may serve as a novel serological marker for assessing cardiovascular disease risk in essential hypertension patients.

Our study population consisted primarily of essential hypertension patients who had not received recent antihypertensive medication; therefore, the results may not be generalizable to patients with secondary hypertension or those on long-term antihypertensive therapy. Several limitations should be acknowledged. First, this was a single-center study, which may limit generalizability compared with multicenter studies. Second, as a retrospective study that excluded patients on antihypertensive medications to avoid confounding effects of different drug classes on circadian rhythm, our findings may not apply to medicated essential hypertension patients.

In summary, our study demonstrates that essential hypertension patients with abnormal circadian blood pressure rhythm exhibit higher inflammatory factor levels, more severe carotid atherosclerosis, and elevated plasma ox-LDL/ β 2GPI complex levels. $nSBP$, $hs-CRP$, and ox-LDL/ β 2GPI complex are independent risk factors for carotid plaque formation in essential hypertension patients. Inflammatory therapy, and indicate the potential of plasma ox-LDL/ β 2GPI complex as a predictor of cardiovascular disease risk in essential hypertension patients.

Author Contributions: Zhang Juan conceived the primary research objec-

tives and was responsible for study design. Lyu Lulu implemented the study and drafted the manuscript. Zhu Wanjie collected and organized data. Xiao Mingyang and Li Yike performed statistical analysis, created figures and tables, and revised the manuscript. Zhang Juan was responsible for quality control, overall article review, and supervision.

Conflict of Interest: None declared.

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