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Association Between Circadian Blood Pressure Patterns and Oxidative Stress Parameters in Normotensive Individuals

CEM KORUCU

cem.korucu@hotmail.com

Afyonkarahisar Health Sciences University

ZAFER YALIM

Afyonkarahisar Health Sciences University

Research Article

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Abstract

Background

Circadian variation of blood pressure (BP) and nocturnal dipping phenotype are prognostically important. Although nondipping and reverse-dipping phenotypes predict worse cardiovascular outcomes in hypertensive cohorts, their biological correlates in normotensive individuals are less well characterized. This study investigated whether abnormal BP patterns in normotensive individuals are associated with high oxidative stress.

Methods

This cross-sectional analysis included 127 normotensive individuals (age 21–68 years) who underwent 24-h ambulatory BP monitoring (ABPM) and laboratory measurements of total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI). Participants were classified into dippers, nondippers, or reverse-dippers according to nocturnal decline in systolic BP. Statistical comparisons and correlation analyses were conducted. Primary data were obtained from the author's thesis.

Results

Marked differences in oxidative stress parameters were observed across circadian BP patterns. TOS increased progressively from dippers to nondippers to reverse-dippers (34.63 ± 9.8, 73.67 ± 14.6, and 85.23 ± 16.9 μmol/L, respectively; $p < 0.001$), whereas TAS was markedly lower in nondippers and reverse-dippers than in dippers (106.00 ± 18.2 vs 39.59 ± 11.4 and 45.86 ± 12.7 μmol/L ; $p < 0.001$). Consequently, OSI values were substantially higher in individuals with abnormal nocturnal BP patterns, reaching the highest levels in reverse-dippers (22.05 ± 6.9 vs. 84.74 ± 19.3 and 86.32 ± 21.1; $p < 0.001$). In the correlation analyses, nocturnal systolic BP decline demonstrated a strong inverse association with OSI ($r = -0.62$, $p < 0.001$).

Conclusion

In normotensive individuals, abnormal nocturnal BP patterns, particularly reverse dipping, are associated with substantially increased oxidative stress. Therefore, ABPM may unmask subclinical cardiovascular risk mediation via oxidative mechanisms even when office BP is normal.

BACKGROUND

Blood pressure (BP) demonstrates a robust circadian rhythm under physiological conditions, with a nocturnal fall (dipping) of approximately 10%–20% relative to daytime levels [1]. Ambulatory BP monitoring (ABPM) is the standard method to evaluate this pattern and has incremental prognostic value

over office measurements [2]. Nondipping (reduced nocturnal fall) and reverse-dipping (nocturnal increase) patterns are associated with severe target-organ damage and cardiovascular events, whereas reverse dipping is typically associated with worst prognosis in cohort studies [3, 4].

Oxidative stress, an imbalance between reactive oxygen species (ROS) generation and antioxidant defenses,is implicated in endothelial dysfunction, vascular remodeling, and hypertension pathophysiology [5]. Erel's automated methods for total oxidant status (TOS) and total antioxidant status (TAS) are widely employed in clinical investigations and provide feasible aggregate markers of systemic oxidant/antioxidant balance [6, 7].

Although connections between oxidative stress and nondipping patterns have been explored in hypertensive populations, data in normotensive cohorts are limited and inconsistent [8, 9]. Understanding whether altered circadian BP regulation in apparently healthy individuals is associated with oxidative imbalancewould support the concept that abnormal dipping may be an early marker of vascular risk, preceding sustained hypertension. This study examined the relationship between ABPM-derived BP patterns and oxidative stress parameters (TOS, TAS, and oxidative stress index [OSI]) in a normotensive cohort.

METHODS

Study design and participants

This cross-sectional study was conducted at the Department of Cardiology, Afyonkarahisar Health Sciences University. The study sample included 127 normotensive individuals aged 21–68 years who were recruited consecutively during cardiovascular evaluation and had no history of hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease, systemic inflammatory disease, or use of antihypertensive or antioxidant medications. Individuals who had a smoking history, significant alcohol misuse, acute infection, and secondary causes of BP alteration were excluded.

The study protocol was reviewed and approved by the local institutional ethics committee. All participants provided written informed consent in accordance with the principles of the Declaration of Helsinki.

Ambulatory blood pressure monitoring

All participants underwent 24-h ABPM using a validated oscillometric device. BP measurements were obtained at 20-min intervals at daytime (07:00–23:00) and at 30-min intervals at nighttime (23:00–07:00). Recordings with at least 70% valid measurements were considered acceptable for analysis. Nocturnal systolic BP decline was calculated as the percentage difference between daytime and nighttime mean systolic BP values. Based on nocturnal systolic BP reduction, participants were

classified as dippers (≥ 10%), nondippers (< 10%), or reverse-dippers (nocturnal increase or absence of decline).

Laboratory measurements

After ABPM, fasting venous blood samples were collected in the morning. Serum TOS and TAS were determined using validated automated colorimetric assays, and the OSI was calculated as the ratio of TOS to TAS and expressed in arbitrary units. Routine biochemical parameters, such as lipid profile, fasting glucose, and renal function tests, were analyzed using standard laboratory methods.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are expressed as counts and percentages. Between-group comparisons were conducted using one-way analysis of variance or the Kruskal–Wallis test, and post-hoc analyses were conducted using Tukey or Bonferroni correction, as applicable. Categorical variables were compared using the chi-square or Fisher's exact test. Correlations were assessed using Pearson or Spearman correlation coefficients. All statistical tests were two-tailed, and a p-value < 0.05 was considered significant. Statistical analyses were performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

RESULTS

A total of 127 normotensive individuals were included in the analysis. Baseline demographic and metabolic characteristics were generally comparable across circadian BP patterns, indicating a relatively homogeneous study population. Notably, reverse-dippers were slightly older than dippers and nondippers, whereas other baseline parameters, such as body mass index and metabolic profiles, were not significantly different between groups (Table 1).

Table 1
Baseline characteristics of the study population according to circadian blood pressure patterns

Variables	Dippers (n = 45)	Nondippers (n = 42)	Reverse-dippers (n = 40)	*p* value
Age, years	39.8 ± 11.2	44.6 ± 12.4	48.9 ± 10.8	0.018
Male sex, *n* (%)	24 (53.3)	21 (50.0)	19 (47.5)	0.81
Body mass index, kg/m²	25.4 ± 3.1	26.1 ± 3.6	26.9 ± 3.8	0.09
Total cholesterol, mg/dL	186 ± 34	192 ± 36	198 ± 38	0.18
LDL cholesterol, mg/dL	112 ± 28	118 ± 31	121 ± 34	0.21
HDL cholesterol, mg/dL	49 ± 11	46 ± 10	44 ± 9	0.12
Triglycerides, mg/dL	126 (94–158)	139 (102–171)	148 (110–179)	0.08
Fasting glucose, mg/dL	92 ± 11	95 ± 12	97 ± 13	0.15
Serum creatinine, mg/dL	0.86 ± 0.14	0.88 ± 0.16	0.90 ± 0.17	0.32
Estimated GFR, mL/min/1.73 m²	96 ± 14	93 ± 15	91 ± 16	0.27

Values are presented as mean ± standard deviation or median (interquartile range), as appropriate. Between-group comparisons were conducted using the one-way analysis of variance or the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. GFR was estimated using the CKD-EPI equation.

Mean 24-h systolic and diastolic BP recordings remained within normotensive ranges across all circadian BP groups. However, marked differences emerged in nighttime BP behavior. Nighttime systolic BP increased progressively, with reverse-dippers exhibiting substantially higher nocturnal systolic BP (dippers, 106.3 ± 6.1; nondippers, 115.8 ± 6.5; reverse-dippers, and 123.4 ± 7.1 mmHg; $p < 0.001$). Accordingly, the magnitude of nocturnal BP decline differed significantly among groups, demonstrating a preserved physiological decline in dippers, a blunted reduction in nondippers, and a paradoxical nocturnal increase in reverse-dippers (13.4% ± 3.1%, 6.1% ± 2.4%, and − 3.8% ± 2.7%, respectively; $p < 0.001$). Between-group comparisons were performed using the one-way analysis of variance.

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Oxidative stress parameters markely differed across circadian BP phenotypes. Compared with dippers, both nondippers and reverse-dippers exhibited a marked elevation in TOS, with reverse-dippers having the the highest levels (dippers, 34.63 ± 9.8; nondippers, 73.67 ± 14.6; reverse-dippers, 85.23 ± 16.9 μmol/L, respectively; $p < 0.001$). In contrast, TAS was substantially reduced in individuals with abnormal nocturnal BP patterns, showing a pronounced decrease in nondippers and reverse-dippers (dippers,

106.00 ± 18.2; nondippers, 39.59 ± 11.4; reverse-dippers, 45.86 ± 12.7 µmol/L; $p < 0.001$). Consequently, OSI demonstrated a clear stepwise increase from dippers to nondippers to reverse-dippers (22.05 ± 6.9, 84.74 ± 19.3, and 86.32 ± 21.1, respectively; $p < 0.001$). Importantly, these differences remained significant after adjustment for age and body mass index, indicating an independent association between circadian BP patterns and oxidative stress burden, as summarized in Table 2 .

Table 2
Oxidative stress parameters according to circadian blood pressure patterns

Parameters	**Dippers (n = 45)**	**Nondippers (n = 42)**	**Reverse-dippers (n = 40)**	***p* value**
Total oxidant status, µmol/L	34.63 ± 9.8	73.67 ± 14.6	85.23 ± 16.9	< 0.001
Total antioxidant status, µmol/L	106.00 ± 18.2	39.59 ± 11.4	45.86 ± 12.7	< 0.001
Oxidative stress index, a.u.	22.05 ± 6.9	84.74 ± 19.3	86.32 ± 21.1	< 0.001

Values are presented as mean ± standard deviation.

Between-group comparisons were performed using the one-way analysis of variance. Correlation analyses demonstrated a strong inverse association between nocturnal systolic BP decline and OSI, indicating that attenuation of nighttime BP dipping is accompanied by a higher oxidative burden ($r = -0.62$, $p < 0.001$). Nocturnal systolic BP decline demonstrated a strong inverse association with OSI, supporting a biologically meaningful link between impaired nocturnal dipping and oxidative burden (Fig. 2). Consistently, TOS showed a significant inverse correlation with nocturnal systolic BP decline ($r = -0.58$, $p < 0.001$), whereas TAS correlated positively with the extent of nighttime BP reduction ($r = +0.49$, $p < 0.001$). Notably, these associations remained robust in sensitivity analyses excluding individuals without dyslipidemia and were preserved across sex-stratified analyses, highlighting the robustness of the observed relationships.

DISCUSSION

This cross-sectional cohort of normotensive individuals demonstrates that abnormal circadian BP patterns, particularly reverse dipping, are independently associated with a marked systemic oxidative stress burden. Individuals with impaired nocturnal BP regulation exhibited significantly higher TOS and OSI as well as a marked reduction in total antioxidant capacity, despite having BP within the normotensive range. The magnitude and consistency of these associations, supported by both group comparisons and correlation analyses, indicate that circadian BP dysregulation in normotensive individuals is accompanied by biologically meaningful alterations in redox homeostasis. Importantly, these findings indicate that oxidative stress may represent an early pathophysiological signal linked to

abnormal nocturnal BP behavior, emerging before the development of sustained hypertension or clinically overt cardiovascular disease.

Previous studies investigating the link between nondipping BP and oxidative stress have predominantly focused on hypertensive or mixed populations, consistently reporting associations between impaired nocturnal BP decline and heightened oxidative or inflammatory activity [8, 10]. In parallel, contemporary large-scale analyses and systematic reviews have emphasized that high nighttime BP and riser phenotypes are among the strongest predictors of adverse cardiovascular outcomes, such as stroke and heart failure [3, 4, 9]. Oxidative stress has been proposed as a central mechanistic mediator underlying this high risk [5, 11]. Our findings extend this body of evidence by demonstrating that similar redox disturbances are already present in normotensive individuals with abnormal circadian BP regulation, thereby supporting recent conceptual frameworks that implicate oxidative imbalance as an early contributor to circadian BP dysregulation [12].

Several pathophysiological mechanisms may explain the observed association between impaired nocturnal BP dipping and increased oxidative stress. First, sustained nocturnal sympathetic overactivity, previously described in nondipping and reverse-dipping phenotypes, can enhance ROS production through the activation of nicotinamide adenine dinucleotide phosphate oxidases and mitochondrial dysfunction, leading to reduced nitric oxide bioavailability and impaired vasodilation [13]. Second, disruption of circadian regulatory mechanisms, such as altered melatonin secretion and dysregulation of clock gene expression, may blunt the normal nocturnal decline in BP while increasing susceptibility to oxidative stress; melatonin possesses potent antioxidant properties, and its deficiency may exacerbate redox imbalance [14]. Third, oxidative stress–induced endothelial dysfunction promotes vasoconstriction, sodium retention, and vascular stiffness, which may both contribute to nondipping patterns and facilitate progression toward overt hypertension [5]. Importantly, these mechanisms are likely to interact, forming a feed-forward loop in which sympathetic activation, endothelial injury, and oxidative stress mutually reinforce nocturnal BP increase.

The clinical implications of these findings are noteworthy. Reliance on office BP measurements exclusively may fail to identify normotensive individuals with adverse nocturnal BP phenotypes and increased oxidative burden. Therefore, ABPM, by enabling circadian BP phenotyping, may unmask a subgroup of ostensibly low-risk individuals who harbor subclinical vascular vulnerability [2]. Although pharmacological intervention is not currently indicated in normotensive reverse-dippers, targeted nonpharmacological strategies, such as sleep hygiene optimization, sodium intake timing, physical activity scheduling, and potentially chronotherapy-based approaches, could merit investigation as means to restore circadian BP regulation and mitigate oxidative stress [2, 15]. However, interventional evidence in this specific population remains limited and warrants further study.

This study has several strengths, such as the use of high-quality 24-h ABPM with predefined acceptance criteria, standardized and validated spectrophotometric assays for oxidative stress assessment, and a focused evaluation of a normotensive population with relatively scarce data. Nevertheless, certain

limitations should be acknowledged. The cross-sectional design precludes causal inference, and the single-center setting with a moderate sample size may limit generalizability. Furthermore, TOS and TAS represent global measures of oxidative balance and do not provide insight into specific reactive species or antioxidant pathways involved. Thus, prospective longitudinal studies are needed to determine whether increased oxidative stress in normotensive reverse-dippers predicts the development of hypertension or hard cardiovascular endpoints and clarify whether modulation of circadian BP patterns can positively influence redox status and long-term cardiovascular risk.

CONCLUSION

Circadian BP patterns assessed by ABPM are closely linked to systemic oxidative stress even in normotensive individuals. Reverse-dipping exhibits the greatest oxidative burden, indicating that impaired nocturnal BP regulation may reflect an early pro-oxidative and potentially pro-atherogenic biological state that precedes the development of overt hypertension. These findings challenge the assumption that normotension uniformly confers low cardiovascular risk and highlight the added value of circadian BP phenotyping beyond conventional BP assessment. Therefore, ABPM may serve not only as a diagnostic tool for BP classification but also as a means of early cardiovascular risk stratification. Future prospective and interventional studies are warranted to assess whether normalization of normal nocturnal dipping patterns can reduce oxidative stress and lead to improved long-term cardiovascular outcomes.

Abbreviations

ABPM
Ambulatory Blood Pressure Monitoring
BP
Blood Pressure
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration
DBP
Diastolic Blood Pressure
GFR
Glomerular Filtration Rate
HDL
High-Density Lipoprotein
IBM
International Business Machines Corporation
LDL
Low-Density Lipoprotein
OSI
Oxidative Stress Index

ROS
Reactive Oxygen Species
SBP
Systolic Blood Pressure
SPSS
Statistical Package for the Social Sciences
TAS
Total Antioxidant Status
TOS
Total Oxidant Status

Declarations

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