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Correlations of Circadian Rhythm Disorder of Blood Pressure with Arrhythmia and Target Organ Damage in Hypertensive Patients

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACDE **Lixiong Zeng**
ABEG **Zhihui Zhang**
ABF **Xiaoyan Wang**
BCE **Shan Tu**
CDF **Fei Ye**

Department of Cardiology, The Third Xiangya Hospital of Central South University, Changsha, Hunan, P.R. China

Corresponding Author: Zhihui Zhang, e-mail: Zhangzhihui0869@126.com

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Background: The aim of this study was to investigate the correlations of circadian rhythm disorder of blood pressure with arrhythmia and target organ damage in hypertensive patients.

Material/Methods: A total of 198 patients admitted and treated in our hospital from May 2018 to April 2019 were selected to receive 24-h ambulatory blood pressure monitoring. The nighttime blood pressure decrease rate is 0–10% in people with normal circadian rhythm of blood pressure. In the present study, we divided patients into a normal circadian rhythm group (normal circadian rhythm of blood pressure, n=132) and a circadian rhythm disorder group (circadian rhythm disorder of blood pressure, n=66) according to the circadian rhythm of blood pressure. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean pulse pressure (PP) were observed, and dynamic electrocardiography was performed to observe the status of arrhythmia. Finally, the degree of damage to target organs such as heart, brain, and kidney was compared.

Results: The circadian rhythm disorder group had remarkably higher daytime SBP (d-SBP), daytime DBP (d-DBP), and daytime PP (d-PP) but clearly lower nighttime SBP (n-SBP), nighttime DBP (n-DBP), and nighttime PP (n-PP) than in the normal circadian rhythm group ($P<0.0001$). The detection rate of arrhythmia and the degree of target organ damage were clearly higher in the circadian rhythm disorder group compared with the normal circadian rhythm group ($P<0.0001$). Moreover, the incidence rates of heart disease, cerebrovascular disease, and nephropathy were higher in the circadian rhythm disorder group than in the normal circadian rhythm group ($P<0.0001$).

Conclusions: The circadian rhythm disorder of blood pressure in hypertensive patients probably increases the risk of arrhythmia and worsens the target organ damage, so attention should be paid to the adjustment of disordered blood pressure rhythm in hypertensive patients in clinical practice.

MeSH Keywords: **Arrhythmias, Cardiac • Blood Pressure • Circadian Rhythm • Hypertension**

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Background

The incidence rate of hypertension is rising constantly around the world, and the patients tend to be younger with the improvement of people's living standard and change in daily dietary structure [1,2]. Although current drug therapies can significantly control hypertension, they still have certain adverse effects on patients, such as increased heart rate, abnormal lipid metabolism, and impaired renal function [3,4]. The incidence of arrhythmia is significantly increased in hypertensive patients, seriously influencing their quality of life [5]. The circadian rhythm of blood pressure of the hypertensive patients can be reflected by 24-hour ambulatory blood pressure monitoring [6]. A study has proven that the circadian rhythm of blood pressure is closely associated with arrhythmia and target organ damage, and this finding has been accepted by the medical community [7]. In the present study, we assessed the circadian rhythm of blood pressure of hypertensive patients and analyzed its correlations with the incidence of complications and prognosis, hoping to provide a basis for patient care.

Material and Methods

General data

A total of 198 patients admitted and treated in our hospital from May 2018 to April 2019 were enrolled in this research. Inclusion criteria were: (1) diagnosed with hypertension [8], (2) clear consciousness and be able to communicate normally, and (3) signed the informed consent. Exclusion criteria were: (1) congenital diseases or malignant tumors and (2) secondary hypertension. The circadian rhythm of blood pressure of the patients was observed and divided into [9] (1) dipper type – nighttime blood pressure decrease rate is 10–20%, (2) non-dipper type – nighttime blood pressure decrease rate is <10%, (3) reverse-dipper type – nighttime blood pressure decrease rate is a negative value, and (4) extreme-dipper type – nighttime blood

pressure decrease rate is >20% according to the nighttime blood pressure decrease rate=(daytime blood pressure – nighttime blood pressure)/daytime blood pressure×100%, in which the non-dipper type have normal circadian rhythm of blood pressure and the others have circadian rhythm disorder of blood pressure. The patients were divided into a normal circadian rhythm group (normal circadian rhythm of blood pressure, n=132) and a circadian rhythm disorder group (circadian rhythm disorder of blood pressure, n=66) according to the circadian rhythm of blood pressure ($P>0.05$) (Table 1). This study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University. Signed written informed consents were obtained from all participants before the study began.

Measurement of blood pressure

A non-invasive portable ambulatory blood pressure monitor was utilized to record the 24-h ambulatory blood pressure of the 2 groups of patients. The patients were guided to bind the cuff to the left upper arm, and the frequency of measurement was set as follows: once every 60 min in the daytime (from 8:00 a.m. to 8:00 p.m.) and once every 120 min at night (from 8:01 p.m. to 7:59 a.m.). Patients were instructed to keep the left arm relaxed during the monitoring, they could have normal physiological activities but should avoid strenuous exercises, and they needed to keep calm emotions instead of greatly fluctuated emotions. Any discomfort was recorded in a timely manner. Relevant parameters and indexes to be recorded included: 24-h mean systolic blood pressure (24 h-mSBP), daytime mSBP (d-SBP), nighttime mSBP (n-SBP), 24-h mean diastolic blood pressure (24 h-mDBP), daytime mDBP (d-DBP), nighttime mDBP (n-DBP), 24-h mean pulse pressure (24 h-PP), daytime PP (d-PP), and nighttime PP (n-PP).

Examination of target organ damage

With the patient in left lateral decubitus position, echocardiography was performed using ACUSON SC2000

Table 1. General data of research subjects.

Item	Normal circadian rhythm group (n=66)	Circadian rhythm disorder group (n=132)	P
Age (years old)	40–78	40–75	
Gender (Male/Female)	36/30	73/59	0.771
Average age (years old)	58.8±7.4	58.4±7.8	0.724
BMI(kg/m ²)	22.6±1.5	22.6±1.2	0.406
Smoking [n (%)]	16 (24.2)	33 (25.0)	0.953
Drinking [n (%)]	24 (36.4)	49 (37.1)	0.958

BMI – body mass index.

Table 2. Comparison of DBP, SBP and PP measured between the two groups of patients (mmHg).

	Normal circadian rhythm group	Circadian rhythm disorder group	P
24 h-mDBP	88.4±3.2	88.9±3.7	0.821
d-DBP	91.6±3.2	97.2±3.3	<0.0001
n-DBP	86.3±3.5	80.5±3.2	<0.0001
24 h-mSBP	151.7±5.2	151.5±5.2	0.826
d-SBP	144.4±5.5	159.8±4.6	<0.0001
n-SBP	149.5±5.5	143.1±5.4	<0.0001
24 h-PP	68.7±3.6	68.9±3.7	0.624
d-PP	71.4±3.6	77.7±3.8	<0.0001
n-PP	66.6±3.4	60.3±3.5	<0.0001

DBP – diastolic blood pressure; SBP – systolic blood pressure; PP – pulse pressure.

ultrasonic diagnostic equipment (Siemens, Germany), during which left ventricular end-diastolic diameter (LVEDD), interventricular septum thickness (IVST), and end-diastolic left ventricular posterior wall thickness (LVPWT) were measured. The left ventricular mass (LVM) was calculated as: $LVM=1.04 \times [(LVEDD+IVST+LVPWT)^3 - LVEDD^3] - 14$. Body surface area (BSA) = $0.0061 \times \text{body height} + 0.0128 \times \text{body weight} - 0.1529$. Finally, the LVM index (LVMI) was calculated as: $LVMI=LVM/BSA$ [10]. The patients were subjected to 24-h cardiac rhythm monitoring through a synchronous 12-lead dynamic electrocardiogram system, and the incidence of arrhythmia was observed. The patients were instructed to lie in supine position with the head turned to the contralateral side to expose the carotid artery. Then, ultrasonography for the carotid intima was performed using a G60 color Doppler ultrasonic apparatus (Siemens, Germany), and the carotid intima-media thickness (IMT) was measured 3 times to calculate the mean value. Venous blood (5 mL) was drawn to assess the serum creatinine (SCr) level via a fully-automatic biochemistry analyzer and to calculate the creatinine clearance rate: $\text{creatinine clearance rate}=(140-\text{age}) \times \text{body weight}/72 \times \text{SCr}$. For women, $\text{creatinine clearance rate}=\text{calculation} \times 0.85$ [11].

Statistical analysis

Statistical Product and Service Solutions (SPSS) 19.0 (SPSS, Inc., Chicago, IL, USA) software was utilized to process the data. We performed *t* tests to compare the measurement data between groups, and we used the chi-square (χ^2) test for analysis of enumeration data. $P < 0.05$ was considered to be statistically significant.

Results

General clinical data

There were no significant differences in general data between the 2 groups ($P > 0.05$), as shown in Table 1.

DBP measured in the observation group and normal circadian rhythm group

In circadian rhythm disorder group, d-DBP was remarkably higher than in the normal circadian rhythm group, while n-DBP was notably lower than in the normal circadian rhythm group ($P < 0.0001$) (Table 2).

SBP measured in the 2 groups of patients

The circadian rhythm disorder group had significantly higher d-SBP and significantly lower n-SBP compared with the normal circadian rhythm group ($P < 0.0001$) (Table 2).

PP measured in the 2 groups of patients

The d-PP was significantly higher and n-PP was significantly lower in the circadian rhythm disorder group than in the normal circadian rhythm group ($P < 0.0001$) (Table 2).

Incidence rate of arrhythmia in the 2 groups of patients

Compared to the normal circadian rhythm group, the circadian rhythm disorder group had significantly higher incidence rates of multiple types of arrhythmia, including atrial arrhythmia (atrial premature beats, atrial tachycardia, atrial flutter, atrial fibrillation), ventricular arrhythmia (premature ventricular contraction, ventricular tachycardia, ventricular flutter, ventricular fibrillation), atrioventricular block (degree I, II, III),

Table 3. Comparison of arrhythmia and degree of target organ damage in the two groups of patients.

	Normal circadian rhythm group	Circadian rhythm disorder group	P
Atrial arrhythmia	17 (12.9)	38 (57.6)	<0.0001
Ventricular arrhythmia	9 (6.8)	21 (31.8)	<0.0001
Atrioventricular block	6 (4.6)	19 (28.8)	<0.0001
Bundle branch block	5 (3.8)	18 (27.3)	<0.0001
LVMI (g/m ²)	90.6±3.8	83.6±3.6	<0.0001
IMT (mm)	0.8±0.4	1.2±0.6	<0.0001
Creatinine clearance rate	86.1±3.6	70.7±3.6	<0.0001
Heart disease	19 (14.4)	40 (60.6)	<0.0001
Cerebrovascular disease	8 (6.1)	16 (24.2)	0.0001
Nephropathy	4 (3.0)	13 (19.7)	<0.0001

LVMI – left ventricular mass index; IMT – carotid intima-media thickness.

and bundle branch block (complete left bundle branch block, complete right bundle branch block, left anterior hemiblock, left posterior hemiblock) ($P<0.0001$) (Table 3).

Degree of target organ damage in the 2 groups of patients

Compared to the normal circadian rhythm group, the circadian rhythm disorder group had significantly lower LVMI and creatinine clearance rates and significantly higher IMT ($P<0.0001$) (Table 3).

Target organ damage in the 2 groups of patients

The prevalence rates of heart disease, cerebrovascular disease, and nephropathy were significantly higher in the circadian rhythm disorder group than in the normal circadian rhythm group ($P<0.0001$) (Table 3).

Discussion

Hypertension, the most common cardiovascular syndrome encountered in clinical practice, can be classified into essential hypertension and secondary hypertension [12]. The morbidity rate of hypertension can be up to 20% or higher in some countries [13]. The onset of the disease involves many factors, including diet, infection, psychological pressure, medicine, and social factors, which lead to changes in the cardiac and vascular function and structure of the patients, seriously affecting the patient's quality of life [14,15]. As 24-h ambulatory blood pressure monitoring is widely applied clinically, it has become an important focus of research on circadian rhythm disorder of blood pressure in hypertensive patients.

Sympathetic nervous activity in the human body is the weakest at night when the muscles are relaxed sufficiently, and peripheral vascular resistance is also minimized, and during this period blood pressure is a good indicator of the degree of disease [16]. The results of the present research showed that the circadian rhythm disorder group had remarkably higher d-SBP, d-DBP, and d-PP but lower n-SBP, n-DBP, and n-PP than in the normal circadian rhythm group, which may be related to the strengthened stress-sensitivity of sympathetic nervous system activity and decreased function of vagus nerve in patients with circadian rhythm disorder of blood pressure, suggesting that such patients have severe hypertension.

A study demonstrated that circadian rhythm disorder of blood pressure can serve as a predictor of cardiovascular risk and is positively correlated with the incidence of arrhythmia [17]. We found that the incidence rates of arrhythmia, including atrial arrhythmia, ventricular arrhythmia, atrioventricular block, and bundle branch block, were prominently higher in the circadian rhythm disorder group than in the normal circadian rhythm group ($p<0.05$). The reason for this is that receptors in the human body are maintained at a low threshold in normal resting state, during which persistent impulses are transmitted to the center, thus maintaining normal blood pressure. In patients with circadian rhythm disorder of blood pressure, the blood pressure is elevated for a short time, which can stimulate the receptors to stay in a high threshold state and generate excitement. Therefore, the impulses are increased, baroreflex is enhanced, and more adverse effects are produced on the vascular center, resulting in nighttime hemodynamic change, increased left ventricle load, decreased cardiac function, and altered myocardial stress, excitability, automaticity, and conductivity, thereby increasing susceptibility to various types of arrhythmia and the incidence of ventricular arrhythmia [18]. In the process of cardiac remodeling, circadian rhythm

disorder of blood pressure induces left ventricular hypertrophy and left atrial enlargement, thus damaging the atrial vagus nerve, enhancing atrial automaticity, and triggering more atrial arrhythmia.

Clinically, circadian rhythm of blood pressure is commonly regarded as an indicator for the assessment of target organ damage. The occurrence of the circadian rhythm disorder of blood pressure suggests target organ damage [19,20]. We found that the circadian rhythm disorder group had clearly higher prevalence rates of heart disease, cerebrovascular disease, and nephropathy compared with the normal circadian rhythm group. Moreover, the circadian rhythm disorder group had evidently lower LVMI and creatinine clearance rate but obviously greater IMT than in the normal circadian rhythm group ($P<0.05$). This is because the sympathetic nerves of people with circadian rhythm disorder of blood pressure are excessively excited and the levels of norepinephrine, plasminogen activator, and C-reactive protein are increased, thus damaging the target organs. Circadian rhythm disorder of blood pressure imposes a high load on the heart, during which cardiac remodeling and myocardial sclerosis are accelerated, easily causing left ventricular hypertrophy. In addition, the renin-angiotensin-aldosterone system is excessively activated, in which aldosterone leads to cardiac interstitial hyperplasia, and angiotensin II

directly stimulates the cardiomyocytes, ultimately causing cardiac hypertrophy and increasing the incidence rate of heart disease. The carotid artery is the window of the medium-sized arteries in the whole body, and in the case of circadian rhythm disorder of blood pressure, vascular injury is exacerbated, thereby thickening the carotid intima-media. In addition, more C-reactive proteins will speed up the carotid atherosclerosis, which is prone to inducing cerebrovascular disease. When circadian rhythm disorder of blood pressure occurs, the glomerular basement membrane is thickened and perfusion is increased, causing impairment of renal tissues.

Conclusions

Circadian rhythm disorder of blood pressure is closely correlated with arrhythmia and target organ damage in hypertensive patients. Therefore, close attention should be paid to the circadian rhythm of blood pressure in these patients, and disordered circadian rhythm needs to be corrected in time during the treatment of hypertension so as to guarantee good prognosis.

Conflict of interest

None.

References:

- Lacruz ME1, Kluttig A, Hartwig S et al: Prevalence and incidence of hypertension in the general adult population: Results of the CARLA-Cohort Study. *Medicine (Baltimore)*, 2015; 94(22): e952
- Austin ED, Loyd JE, Phillips JR: Genetics of pulmonary arterial hypertension. *Semin Respir Crit Care Med*, 2009; 30: 386–98
- Forouzanfar MH, Liu P, Roth GA et al: Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA*, 2017; 317: 165–82
- Jia CF, Wang ZQ, Sun XX et al: Ascending aortic distensibility and target organ damage in primary hypertension without diabetes. *Int J Cardiovasc Imaging*, 2017; 33: 1245–51
- Kang KT, Chiu SN, Weng WC et al: Comparisons of office and 24-hour ambulatory blood pressure monitoring in children with obstructive sleep apnea. *J Pediatr*, 2017; 182: 177–83
- de Simone G, Wang W, Best LG et al: Target organ damage and incident type 2 diabetes mellitus: The Strong Heart Study. *Cardiovasc Diabetol*, 2017; 16: 64
- Niiranen TJ, Lin H, Larson MG, Vasan RS: Familial clustering of hypertensive target organ damage in the community. *J Hypertens*, 2018; 36: 1086–93
- Fryar CD, Ostchega Y, Hales CM et al: Hypertension prevalence and control among adults: United States, 2015–2016. *NCHS Data Brief*, 2017; (289): 1–8
- Cifkova R: Should 24-hour ambulatory blood pressure monitoring become part of regular checkup in women with previous preeclampsia? *Hypertension*, 2018; 71: 59–60
- Tripepi G, Pannier B, D'Arrigo G et al: Reappraisal in two European cohorts of the prognostic power of left ventricular mass index in chronic kidney failure. *Kidney Int*, 2017; 91: 704–10
- Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron*, 1976; 16: 31–41
- Liu DF, Li SM, Zhu QX, Jiang W: The involvement of miR-155 in blood pressure regulation in pregnant hypertension rat via targeting FOXO3a. *Eur Rev Med Pharmacol Sci*, 2018; 22: 6591–98
- Qaseem A, Wilt TJ, Rich R et al: Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med*, 2017; 166: 430–37
- Lu J, Lu Y, Wang X et al: Prevalence, awareness, treatment, and control of hypertension in China: Data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). *Lancet*, 2017; 390: 2549–58
- Han H, Fang X, Wei X et al: Dose-response relationship between dietary magnesium intake, serum magnesium concentration and risk of hypertension: A systematic review and meta-analysis of prospective cohort studies. *Nutr J*, 2017; 16: 26
- Che X, Mou S, Zhang W et al: The impact of non-dipper circadian rhythm of blood pressure on left ventricular hypertrophy in patients with non-dialysis chronic kidney disease. *Acta Cardiol*, 2017; 72: 149–55
- Ma L, Li Y: The effect of depression on sleep quality and the circadian rhythm of ambulatory blood pressure in older patients with hypertension. *J Clin Neurosci*, 2017; 39: 49–52
- Waligora M, Tyrka A, Miszalski-Jamka T et al: Right atrium enlargement predicts clinically significant supraventricular arrhythmia in patients with pulmonary arterial hypertension. *Heart Lung*, 2018; 47: 237–42
- Coats A, Jain S: Protective effects of nebivolol from oxidative stress to prevent hypertension-related target organ damage. *J Hum Hypertens*, 2017; 31: 376–81
- Yang Y, Wang Y, Xu J, Gao P: Association between common carotid artery diameter and target organ damage in essential hypertension. *J Hypertens*, 2018; 36: 537–43