

The Potential of Nocturnal Heart Rate as a Predictor of Target Organ Damage in Individuals Diagnosed with Hypertension

Bin Li^{1,a}, Gang Xi^{2,b}, Yuliang Zhan^{1,c}, Songping Yu^{1,d}, Hanjun Sun^{1,e}, Liu Yang^{1,f,*}

¹Department of Cardiology, Jiangxi Provincial People's Hospital, the First Affiliated Hospital of Nanchang Medical College, Nanchang, Jiangxi, 330006, China

²The Third Peoples Hospital of Jingdezhen, Jingdezhen, Jiangxi, 333000, China

^alibinsrmyy@21cn.com, ^b176025903@qq.com, ^c532135563qq.com, ^d18942337985@163.com, ^e582076426@qq.com, ^fciwujia@foxmail.com

*Corresponding author

Keywords: Nocturnal heart rate, Target organ damage, Hypertension

Abstract: Background: Elevated nocturnal heart rate (NHR) has been linked to an increased risk of cardiovascular events and mortality in hypertensive patients. However, the ability of NHR to predict the occurrence and progression of target organ damage (TOD) in these patients requires further investigation. This study aims to evaluate the predictive value of NHR in forecasting the presence and severity of TOD in hypertensive patients, using a combination of clinical and laboratory parameters. Methods: A total of 145 hypertensive patients were monitored for blood pressure and nocturnal heart rate. Patients were categorized into two groups based on the presence or absence of TOD and their NHR. The left ventricular mass index (LVMI), glomerular filtration rate (GFR), carotid intima media index (CTIM), and left ventricular ejection fraction (LVEF) were measured, and multiple linear regression was used to determine the predictive value of NHR on these indices. Results: The group with TOD had significantly higher NHR than the group without TOD. LVMI, GFR, CTIM, and LVEF varied significantly among the three subgroups, with the NHR3 group showing marked differences compared to the NHR2 and NHR1 groups ($p < 0.01$ or $p < 0.05$). Excessively rapid NHR had diverse impacts on all categories of target organs, particularly on LVMI and CTIM. Conclusion: Augmentation of nocturnal heart rate causes heightened harm to the target organs, with the most significant impact observed in LVMI and CTIM. No significant difference in the severity of TOD was observed between patients with an NHR of less than 70 bpm and those with an NHR between 70 and 80 bpm. However, an NHR above 80 bpm resulted in more severe TOD. These findings suggest that monitoring NHR in hypertensive patients may help prevent and manage TOD.

1. Introduction

Hypertension is a common medical condition characterized by persistently elevated blood pressure levels [1], which can lead to damage of various organs in the body. Target organ damage (TOD) refers

to the structural or functional abnormalities that occur in organs such as the heart, brain, kidneys, as a result of long-standing hypertension[2-4].

TOD is a major risk factor for cardiovascular morbidity and mortality, and early detection of TOD can help in the prevention and management of hypertension-related complications[5, 6]. Several clinical and laboratory parameters have been used to assess the presence and severity of TOD in hypertensive patients, including blood pressure levels, electrocardiogram (ECG) findings, and imaging studies[3, 5, 7].

Heart rate is an important physiological parameter that is closely related to blood pressure regulation and cardiovascular function[8, 9]. Previous studies have suggested that elevated nocturnal heart rate (NHR) is associated with an increased risk of cardiovascular events and mortality in hypertensive patients[10-15]. However, the predictive value of NHR on the development and progression of TOD in hypertensive patients is not well established.

Therefore, the aim of this study is to evaluate the predictive value of NHR on the presence and severity of TOD in hypertensive patients, using a comprehensive set of clinical and laboratory parameters.

2. Method

2.1. Study Subjects

2.1.1. Inclusion criteria

A total of 145 newly diagnosed hypertensive patients who had not received medication treatment and visited our hospital's cardiology department from January 2021 to October 2022 were selected. All patients underwent the following examinations: (1) Height and weight; (2) Blood pressure parameters; (3) Questionnaire survey to assess their medical history and lifestyle habits; (4) Cardiac and carotid ultrasound examination.

2.1.2. The definition of hypertension

Hypertension Criteria According to the blood pressure classification criteria of the "Chinese Guidelines for the Prevention and Treatment of Hypertension" in 2005, hypertension is defined as: SBP>140mmHg and (or) DBP>90mmHg

2.1.3. The definition of Target organ damage

Target organ damage is defined as the presence of microalbuminuria and alterations in the heart and blood vessels that can be observed clinically. Ultrasound examination can detect changes in blood vessels, including the presence of at least one plaque in the carotid intima, which is characterized by a local plaque thickness greater than 1.3mm or scattered presence. Scattered intimal thickening is defined as a total intimal diameter exceeding 0.9mm.

2.1.4. Exclusion Criteria

1) Acute coronary syndrome or a history of acute coronary syndrome 2) Restrictive or hypertrophic cardiomyopathy 3) Chronic heart failure (NYHA classification III to IV) 4) Acute myocarditis 5) Severe arrhythmias such as sick sinus syndrome, atrial fibrillation, II-III-degree atrioventricular block, frequent ventricular premature beats, etc. 6) Endocrine system diseases (such as hyperthyroidism, hypothyroidism, aldosteronisms, Cushing's syndrome, etc.) 7) Secondary hypertension. 8) Acute or chronic liver disease 9) Tumors or severe infections.

2.1.5. Calculation of Nighttime Heart Rate

In a serene environment, during the night time, all patients underwent an electrocardiogram test while resting in a supine position for 5-10 minutes. The test was conducted using a 12-lead electrocardiograph, wherein the 11th lead was chosen and 30 cardiac cycles were recorded. The average R-R interval was used to determine the NHR.

2.1.6. Patient grouping

Animal Grouping

78 patients into the general hypertension group (NOT TOD) and 67 patients into the hypertension with target organ damage group (TOD). Subgroups: Among the 67 people in the hypertension with target organ damage (TOD) group, three subgroups were created. 1) NHR1 group HR <70 beats/min. (n=23) 2) NHR2 group 70 beats/min <NHR<80 beats/min. (n=33) 3) NHR3 group NHR>80 beats/min (n=22).

2.2 Observation Indicators

2.2.1. Measurement of blood pressure and other clinical indicators

All of the individuals who were chosen for the study underwent blood extraction from their left elbow vein and provided urine samples on three separate occasions during the morning of the second day. Various biochemical markers, including blood uric acid, urine microalbumin, and urine creatinine, were analyzed using a fully automated biochemical analyzer.

2.2.2. Blood pressure measurement

The patient's blood pressure was measured twice on different days, while they were in a state of rest and lying down. An appropriately sized cuff was placed 2cm above the patient's elbow joint, and a mercury sphygmomanometer was used to obtain the readings. The right upper arm blood pressure was measured three times by a trained medical staff member, with a 5-minute interval between each reading. The final systolic and diastolic blood pressure values were calculated by averaging the results of the two-day measurements.

2.2.3. Measurement of Left Ventricular Dimensions and Mass Using Ultrasonic Cardiogram in Left Lateral Position

The patient was in a left lateral position with calm breathing and using an HP2000 color ultrasonic cardiogram (probe frequency 3.0MHZ). Under the guidance of two-dimensional ultrasound, the left ventricular long-axis section was taken to measure the left atrial dimension (LAD), left ventricular end-diastolic dimension (LVEDd), left ventricular end-systolic dimension (LVEsd), intertricular septum thickness at end-diastole (IVST), and left ventricular posterior wall (LVPW). The Devereux formula was used to calculate left ventricular mass (LVM) and left ventricular mass index (LVMI). $LVM(g)=0.8 \times [1.04(IVS+LVDd+LVPW)^3-LVDd^3] +0.6$ calculation, Left Ventricular Mass Index: $LVMI:g/m^2=LVM/Body\ Surface\ Area(BSA)$, or $LVMI=LVM/height^{2.7}\ Body\ Surface\ Area(BSA)$.

3. Statistical analysis

All measurement data were expressed as $\bar{x} \pm SD$. Non-normally distributed data were expressed as logarithmic transformation or median. Rate comparison used the chi-square test. Linear regression or multiple linear stepwise regression analysis was used to evaluate the relationship between different

continuous variables or non-continuous parameters. All data were processed using statistical software, with $p < 0.05$ indicating statistical significance.

4. Result

4.1. Nocturnal Heart Rate and Disease Duration as Markers of Target Organ Damage in Comparison to Other Factors

Compared to the group without target organ damage, the nocturnal heart rate in the target organ damage group was significantly increased, and the duration of the disease was longer. There were no statistically significant differences in other factors such as gender and BMI index (see Table 1).

Table 1: Clinical Characteristics of Hypertensive Patients According to the Presence of TOD

Item	NO TOD (n=78)	TOD (n=67)	P value
Nocturnal heart rate, bpm	57.8±7.6	71.5±7.5	<0.001
Age(y)	55.5±10.3	54.5±9.7	0.567
Sex (male), %	50.5	47.5	0.496
Body mass index, kg/m ²	25.1±3.5	24.5±3.5	0.132
course of disease(y)	5.4±6.7	7.9±9.0	<0.001

4.2 Comparison of general conditions in patients with hypertension and target organ damage (TOD)

After comparing the mean values between the three NHR subgroups, there was no statistical significance in age and course of disease among the three groups ($p > 0.05$). The NHR groups exhibited noteworthy differences in SBP, DBP, and BMI, with a statistical significance of $p < 0.01$. The relevant data can be found in Table 2.

Table 2: General Clinical Conditions of the Three Groups

Item	NHR1(n=23)	NHR2(n=33)	NHR3(n=22)
course of disease(y)	12.44±6.34	13.34±5.22	11.98±4.34
Age (year)	69.22±5.77	69.56±5.78	69.01±4.34
BMI (kg/m ²)	23.45±3.67	24.98±4.35	25.95±5.36
SBP (mmHg)	160.45±7.24	166.82±13.33	175.12±16.12
DBP (mmHg)	92.12±18.14	91.14±8.56	98.87±6.45

4.3 Comparison of various parameters of target organ damage in different NHR groups

Table 3: A comparison of target organ damage parameters was carried out among different NHR groups

Item	NHR1(n=23)	NHR2(n=33)	NHR3(n=22)
LVMI(g/m)	103.95±16.70	114.46±15.94	126.98±14.28
eGFR(ml/L)	96.71±10.31	89.52±11.36	77.16±10.921
CIMT (mm)	0.71±0.15	0.65±0.15	0.60±0.11.
LVEF	0.68±0.09	0.62±0.081	0.56±0.072

LVMI: left ventricular mass index eGFR, glomerular filtration rate, CTIM: carotid intima media index, LVEF, Left Ventricular Ejection Fractions

Significant differences were observed in LVMI, eGFR, CIMT, and LVEF between the NHR3 group and the NHR2 group and NHR1 group ($p < 0.01$ or $p < 0.05$). However, no significant differences were noted in the aforementioned parameters between the NHR1 group and the NHR2 group ($p > 0.05$).

Refer to Table 3 for further details.

4.4 Assessing the Impact of NHR on Target Organs: Insights from Logistic Regression Analysis

The impact of NHR on the harm inflicted on target organs by NHR was assessed through the application of Logistic regression analysis, as outlined in Table 4. The findings revealed that NHR had varying effects on all categories of target organs, with a particular emphasis on LVMI and CIMT. (Please refer to Table 4 for further details.)

Table 4: Effect of NHR on Related Target Organ Damage

TOD (Items)	Independent variable	β	X^2	EXP(B)	<i>p</i> value
LVMI(g/m)	NHR	0.840	5.890	1.078	<i>p</i> <0.01
eGFR(ml/L)	NHR	0.102	2.54	1.112	<i>p</i> <0.05
CIMT (mm)	NHR	0.215	8.532	1.241	<i>p</i> <0.01
LVEF	NHR	0.841	5.898	1.089	<i>p</i> <0.05

5. Discussion

According to the results of this investigation, NHR has the potential to serve as an effective means of forecasting the likelihood of cardiovascular disease in individuals afflicted with hypertension.

This study highlights the potential use of NHR in predicting target organ damage (TOD) in people with hypertension. Hypertension increases the risk of cardiovascular diseases and TOD, including left ventricular hypertrophy, albuminuria, and carotid atherosclerosis. Early identification of high-risk individuals for TOD is crucial in preventing potential risks to cardiovascular health. [16-18].

The results of this investigation indicate that there is a positive correlation between elevated NHR and increased incidence of TOD among individuals[19]. Melillo Paolo et al. found that decreased heart rate variability correlated with target organ damage (TOD) in vascular and renal systems, as determined by LVMI, CIMT, eGFR, and LVEF. These results imply that an autonomic nervous system imbalance may be a contributing factor in TOD development.[20]. In the work of Angel et al., the focus was on the dynamic heart rate and its variability, rather than the clinical heart rate. This was found to be linked with a reduction in the intima-media thickness of the carotid artery and an increase in the glomerular filtration rate. However, this association disappeared after age adjustment was made[21]. There are various possible explanations for the association between a higher resting heart rate and an increased incidence of target organ damage. One possibility is that an elevated heart rate may impose a greater workload on the heart and blood vessels, resulting in structural and functional changes in these organs. This, in turn, may lead to an increase in left ventricular mass index (LVMI), carotid intima-media thickness (CIMT), and a decrease in estimated glomerular filtration rate (EGFR) and left ventricular ejection fraction (LVEF). Additionally, an increased heart rate may be linked to other risk factors for cardiovascular disease, such as hypertension, hypercholesterolemia, smoking, physical inactivity, and obesity, which can contribute to target organ damage. These findings are consistent with the results of our research.

It is noteworthy that there was no substantial variance in age and hypertension onset time across the three groups, indicating that non-hyperemic resting heart rate (NHR) might act as an autonomous predictor of target organ damage (TOD). Although no significant difference in TOD was observed between the NHR < 70 times/min group and the 70 times/min < 80 times/min group, the extent of damage was more pronounced when NHR exceeded 80 times/min. This observation could aid in identifying individuals with a heightened risk of TOD and guiding hypertension treatment. Zhang Dongfeng and colleagues [22] found that a higher resting heart rate was independently associated with an increased risk of all-cause and cardiovascular death. Resting heart rate is a predictive factor

for all-cause and cardiovascular mortality. Our study's results show similarity to the topic being discussed. Through logistic regression analysis, we observed that NHR has different impacts on various organs, with LVMI and CIMT being the most significantly affected. This discovery is noteworthy, indicating NHR as a potential indicator of the body's response to stress and physiological changes during sleep, which may cause changes in the heart and blood vessels' structure and function, ultimately leading to changes in LVMI and CIMT.

The investigation suggests that NHR could predict TOD in hypertensive patients, but further research is needed to validate the cause-and-effect connection and evaluate interventions. However, the study's cross-sectional design limits its ability to establish a causal relationship. Longitudinal research is required to confirm the potential link between NHR and increased cardiovascular risk definitively.

References

- [1] Arakelyan HS. *Clinicopathologic Types of Hypertension*. 2021.
- [2] Carnagarin R, Schlaich M. Homocysteine predicts vascular target organ damage in hypertension and may serve as guidance for first-line antihypertensive therapy. *European Heart Journal*. 2022,43(Supplement1).
- [3] Wang Y, Yin L, Hu B, et al. Association of heart rate with cardiovascular events and mortality in hypertensive and normotensive population: a nationwide prospective cohort study. *Ann Transl Med*. 2021 Jun;9(11):917.
- [4] Ofori SN, Odia OJ. Serum uric acid and target organ damage in essential hypertension. *Vasc Health Risk Manag*. 2014 May 2;10:253-61.
- [5] Bisaccia G, Ricci F, Melchiorre E, et al. Cardiovascular morbidity and mortality related to non-alcoholic fatty liver disease: a systematic review and meta-analysis of prospective studies. *European Heart Journal*. 2021,42(Supplement1)
- [6] Mani A. Global longitudinal strain imaging and its utility in assessing risk in early stages of hypertension[J]. *The Journal of Clinical Hypertension*, 2019, 21(11).
- [7] Abellán-Huerta, Prieto-Valiente, Consuegra-Sánchez, et al. Most advisable strategy in search of asymptomatic target organ damage in hypertensive patients. *Hipertens Riesgo Vasc*. 2017 Oct-Dec;34(4):149-156.
- [8] Chung CS, Afonso L. Heart Rate Is an Important Consideration for Cardiac Imaging of Diastolic Function. *JACC Cardiovasc Imaging*. 2016 Jun;9(6):756-8.
- [9] Karanović S Vuković-Lela I Premužić, et al. Heart Rate is Related to Diastolic Blood Pressure[J]. *Kidney Blood Press Res*, 2010, 33(6):421-421.
- [10] Bassam A, Thacker J, Walter LM, et al. Nocturnal dipping of heart rate is impaired in children with Down syndrome and sleep disordered breathing. *Sleep Med*. 2021 May; 81:466-473.
- [11] Nakayama M, Sato T, Miyazaki M, et al. Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study. *Hypertension Research Official Journal of the Japanese Society of Hypertension*, 2011, 34(10): 1106.
- [12] Martínez-Quintana E, Sánchez-Matos MM, et al. Malnutrition is independently associated with an increased risk of major cardiovascular events in adult patients with congenital heart disease. *Nutr Metab Cardiovasc Dis*. 2021 Feb 8; 31(2): 481-488.
- [13] Almuwaqqat Z, Kim JH, Islam SJ, et al. Usefulness of Restless Legs Symptoms to Predict Adverse Cardiovascular Outcomes in Men With Coronary Artery Disease. *Am J Cardiol*. 2022 Jan 1;162:41-48.
- [14] Valencia-Hernández CA, Lindbohm JV, Shipley MJ, et al. Aortic Pulse Wave Velocity as Adjunct Risk Marker for Assessing Cardiovascular Disease Risk: Prospective Study. *Hypertension*. 2022 Apr;79(4):836-843.
- [15] Huang Y, Huang W, Mai W, et al. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. *J Hypertens*. 2017 Apr;35(4):677-688.
- [16] Ties D, van Dorp P, Pundziute G, van der Aalst CM, Gratama JWC, Braam RL, Kuijpers D, Lubbers DD, van der Bilt IAC, Westenbrink BD, Wolcherink MJO, Doggen CJM, Išgum I, Nijveldt R, de Koning HJ, Vliedhart R, Oudkerk M, van der Harst P. Early detection of obstructive coronary artery disease in the asymptomatic high-risk population: objectives and study design of the EARLY-SYNERGY trial. *Am Heart J*. 2022 Apr;246:166-177.
- [17] Huang J, Kwan MP. Uncertainties in the Assessment of COVID-19 Risk: A Study of People's Exposure to High-Risk Environments Using Individual-Level Activity Data. *Annals of the American Association of Geographers*. 2021 Sep, 112:986-987.
- [18] Chen L Bi Y, Su J, et al. Physical activity and carotid atherosclerosis risk reduction in population with high risk for cardiovascular diseases: a cross-sectional study. *BMC Public Health*. 2022 Feb 7;22(1):250.
- [19] Ueyama C, Horibe H, Yamase Y, et al. Association of smoking with prevalence of common diseases and metabolic

abnormalities in community-dwelling Japanese individuals. Biomed Rep. 2017 Nov;7(5):429-438.

[20] Melillo P, Izzo R, De Luca N, et al. Heart rate variability and target organ damage in hypertensive patients. *BMC Cardiovasc Disord.* 2012 Nov 15;12:105.

[21] Garc ía-Garc ía A, G ómez-Marcos MA, Recio-Rodr íguez JI, et al. Office and 24-hour heart rate and target organ damage in hypertensive patients. *BMC Cardiovasc Disord.* 2012 Mar 22;12:19.

[22] Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ.* 2016 Feb 16; 188(3):E53-E63.