ORIGINAL RESEARCH

AI/ML to Relationship Between Circadian Rhythm of Blood Pressure and Left Ventricular Hypertrophy in Patients with Hypertension

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ABSTRACT

Objectives • The objective of this experiment was to investigate the relationship between the circadian rhythm of blood pressure and left ventricular hypertrophy (LVH) in patients with hypertension.

Methods • A total of 500 hypertension patients with documented circadian rhythm of blood pressure were selected for this study. The researchers collected general patient data and fasting blood samples. The following parameters were measured within subgroups of hypertensive patients: age, sex ratio, BMI, fasting blood glucose, total cholesterol, triacylglycerol, HDL-C, LDL-C, duration of hypertension, antihypertensive drug usage, and statin intake.

Results • The results of the study showed that LVH hypertension had a significantly higher proportion of grade 3 hypertension compared to non-LVH hypertension ($P < .001$). Additionally, LVH hypertension displayed higher mean systolic blood pressure levels over a 24-hour period ($P = .002$), during daytime ($P = .029$), and during nighttime ($P < .001$). The 24-hour pulse pressure ($P < .001$) and pulse pressure index ($P = 0.001$) were also significantly higher in patients with LVH hypertension. Furthermore, the rate of blood pressure decline at night was significantly lower in the LVH hypertension group compared to the control group ($P < .001$). B-type natriuretic peptide (BNP) levels ($P = .034$) and left ventricular mass index (LVMI) ($P < .001$) were significantly higher in patients with LVH hypertension compared to non-LVH patients.

Conclusions • The findings of this study suggest a close association between hypertensive LVH and the weakening or disappearance of the circadian rhythm of blood pressure. It was also observed that the level of blood pressure classification and plasma BNP levels were increased in patients with LVH hypertension. (*Altern Ther Health Med.* 2024;30(1):58-62).

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INTRODUCTION

Hypertension is an important disease endangering human health.[1] With the continuous development of treatment measures for hypertension, the goal of clinical treatment of hypertension has changed from controlling patients' blood pressure within a reasonable range to restoring patients' normal blood pressure rhythm.[2] Under normal physiological conditions, the blood pressure cycle is 24 hours and fluctuates rhythmically, so it is called circadian rhythm.[3] The circadian rhythm of blood pressure has the characteristics of "two peaks and one valley".[3] The two peak periods of circadian blood pressure occur in the morning from 6:00 to 8:00 and in the afternoon from 16:00 to 18:00 respectively; The period of low blood pressure usually occurs from 2:00 to 3:00 in the morning.[4] Normal blood pressure is maintained at a high level during the day, and gradually decreases after 20:00 at night, maintaining at a low level, that is, it has the characteristics of high blood pressure day and low blood pressure night.[5] Under normal physiological conditions, the 24-hour blood pressure changes have obvious circadian rhythm, and the intraday blood pressure fluctuation pattern is spoon shaped or deep spoon shaped.[6] The circadian rhythm of blood pressure in patients with hypertension will change abnormally, and the circadian rhythm of blood pressure is non-spoon type or reverse spoon type.[7] This change is regulated by the autonomic nervous system, central angiotensin system, vascular endothelial function, renin angiotensin aldosterone system (RAAS), hormones, vasoactive substances, serum cytokine levels, and is affected by salt intake, genetic factors, living conditions, age, and obesity.

Blood pressure (BP) typically exhibits a reliable circadian rhythm, characterized by lower BP during sleep and higher BP during the day. The circadian rhythm variations in hypertension usually manifest in one of the following four patterns: (1) dipping pattern: a 10%-20% average drop in BP during sleep compared to wakefulness; (2) non-dipping pattern: an average decrease in BP of around 10% during sleep compared to wakefulness; (3) reverse-dipping pattern: an average increase in BP during sleep compared to wakefulness; and, (4) extreme-dipping pattern: an average of 20% decrease in BP during sleep compared to wakefulness.

The abnormalities in circadian rhythm are typically associated with the latter three types, with the non-dipping pattern occurring in approximately 36.7% of cases. Both in hypertensive individuals aged 40 or above and young hypertensive patients under 40 years,[8] disrupted circadian rhythm of blood pressure is a risk factor for arrhythmias and target organ damage, particularly with the reverse-dipping pattern, which is associated with the highest incidence of cardiovascular complications. Therefore, optimizing clinical management for hypertensive patients should not only aim at overall blood pressure reduction but also correcting abnormal circadian rhythm patterns.

Essential hypertension is a chronic vascular disease, which is regarded as an independent risk factor for myocardial infarction, left ventricular hypertrophy, and other diseases, and the continuous progress of the disease will damage human blood vessels, heart, kidney, and other target organs, increasing the risk of cardiovascular disease.[9] With the continuous progress of clinical medical treatment, some studies believe that the disappearance or weakening of circadian rhythm of hypertension is an important factor causing target organ damage. At the same time, the significant decrease or abnormal increase of blood pressure at night can increase the risk of complications in patients with essential hypertension.[10,11] Therefore, it is particularly important to observe the 24-hour ambulatory blood pressure changes in patients with essential hypertension.[12]

Left ventricular hypertrophy (LVH) is a compensatory response of the heart of patients with hypertension to long-term sustained elevated blood pressure.[13] It is the most common clinical condition associated with hypertensive heart.[14] Blood pressure circadian rhythm disorder can increase the occurrence of left ventricular hypertrophy, kidney damage, atherosclerotic plaque formation, and even other cardiovascular and cerebrovascular accidents in patients with hypertension, especially in patients with weakened or disappeared dipper pattern.[15] B-type brain natriuretic peptide (BNP) is a brain natriuretic peptide. When ventricular stress, LVH, or volume load increases, the endogenous BNP produced by the left ventricle increases significantly.[16]

MATERIALS AND METHODS

Ambulatory blood pressure monitoring (ABPM)

The non-invasive portable full-automatic ABPM instrument was used to automatically measure once every 20 min during the day from 6:00 to 22:00 according to the setting procedure. It was automatically measured every 30 min from 22:00 to 6:00 at night. Referred to "Chinese blood pressure measurement guidelines" and "ambulatory blood pressure monitoring clinical", and applied the standards recommended in the "consensus of Chinese experts". After continuous monitoring for 24 h, the subjects lived and worked as usual, and the tested upper limbs remained in relatively static state. The number of effective blood pressure monitoring was greater than 85% of the number obtained. Statistical analysis of 24 h blood pressure measurements were conducted, including daytime and nighttime mean systolic and diastolic blood pressure.

Nighttime blood pressure drop rate = (daytime blood pressure average - nighttime blood pressure average) / daytime blood pressure average * 100%. According to the decreased rate of blood pressure at night, the subjects were divided into dipper type group (decreased by 10% - 20%, n = 60), non-dipper type group (0% - 10%, n = 62), super dipper type group (> 20%, n = 58), and anti-dipper type group (< 0%, n = 59). When the systolic blood pressure is inconsistent with the diastolic blood pressure, the systolic blood pressure was deemed to prevail.

Holter monitoring

Quntian and Boying 12 lead monitoring system were adopted. The arrhythmia (including ventricular arrhythmia, supraventricular arrhythmia, first and second atrioventricular block, and ST-T segment changes), and myocardial ischemia were observed and compared between the two groups, and the ST-T segment changes and atrioventricular block were evaluated. The diagnostic criteria of myocardial ischemia were: 80 ms after J-point, ST segment showed horizontal or downward depression of 0.1 mV, duration ≥ 1 min.

Echocardiography

Three cardiac cycles were continuously measured by a specially assigned person: Left ventricular end diastolic diameter (LVEDD), Interventricular septal thickness (IVST), and Left ventricular posterior wall thickness (LVPWT) using Ge Vivid7 color Doppler ultrasound instrument of the United States by American echocardiography Association. Devereux formula used to calculate left ventricular mass (LVM) and left ventricular mass index (LVMI). LVM = 0.8*1.04*[(LVEDD+ IVST+ LVPWT)^3 - LVEDD^3] + 0.6. LVMI(g/m^2) = LVM/ body surface area where body surface area (m^2) = 0.0061 × height(cm)+0.0128* body mass (kg)-0.1529.

Statistical analysis

Data were analyzed with GraphPad 8.0 Software and reported as the mean ± SD. $P < .05$ was considered statistically significant. The differences between the groups were analyzed using Student's t test or two-way ANOVA with repeated measures followed by the Tukey post hoc test.

RESULTS

Baseline clinical data of hypertension subgroups and values of various indicators of hypertension subgroups have been provided in table 1 and table 2 respectively.

Age, sex ratio, BMI, fasting blood glucose, total cholesterol, triacylglycerol, HDL-C, LDL-C, course of hypertension, antihypertensive drugs, and statins in Hypertension subgroups did not have statistically significant difference ($P < .05$).

Table 1. Baseline Clinical Data of this Experiment

Item	Dipper	Non-dipper	Extreme dipper	Anti-dipper
Number of cases (Male / female)	60/62	65/67	61/67	57/61
Age (years)	71.5 ± 8.2	65.7 ± 7.8	71.1 ± 8.5	68.9 ± 7.7
Course of disease (month)	64.2 ± 8.1	64.7 ± 8.9	64.8 ± 8.2	64.5 ± 8.8
Fasting blood glucose (mmol/L)	4.85 ± 0.68	4.67 ± 0.72	4.72 ± 7.8	4.81 ± 0.59
BMI (kg/m^2)	25.6 ± 2.7	26.1 ± 3.1	25.1 ± 2.5	2.63 ± 2.4
Systolic pressure (mm Hg)	155.6 ± 15.1	154.7 ± 14.8	156.1 ± 13.9	154.8 ± 13.8
Diastolic pressure (mm Hg)	90.3 ± 9.1	90.5 ± 9.8	90.7 ± 8.9	91.1 ± 9.5
Total cholesterol (mmol/L)	4.82 ± 1.63	4.78 ± 1.58	4.89 ± 1.52	4.79 ± 1.66
Triacylglycerol (mmol/L)	2.11 ± 0.99	2.08 ± 1.02	2.07 ± 0.97	2.12 ± 0.95

Table 2. Values of Various Indicators of this Experiment

Item	Dipper	Non-dipper	Extreme dipper	Anti-dipper
LDL-C (mmol/L)	3.01 ± 0.48	3.18 ± 0.86	3.17 ± 0.79	3.21 ± 0.74
HDL-C (mmol/L)	1.28 ± 0.42	1.22 ± 0.49	1.19 ± 0.52	1.21 ± 0.47
RAS blocker (case/%)	12 (20.00)	13 (20.97)	12 (20.69)	11 (18.64)
Calcium antagonist (case/%)	18 (30.00)	17 (27.42)	17 (29.31)	16 (27.12)
β Receptor blocker (case/%)	6 (10.00)	5 (8.06)	6 (10.34)	5 (8.47)
Diuretic (case/%)	19 (31.67)	18 (29.03)	17 (29.31)	18 (30.51)
Single compound preparation (case/%)	8 (13.33)	7 (11.29)	8 (13.79)	7 (11.86)
Other antihypertensive drugs (case/%)	3 (5.00)	3 (4.84)	4 (6.90)	3 (5.08)
Statins (case/%)	14 (23.33)	13 (20.97)	12 (20.69)	13 (22.03)

Table 3. LVH Index Level and Detection Rate of LVH in Each Hypertension Subgroups

Item	Dipper	Non-dipper	Extreme dipper	Anti-dipper
Number of cases	122	132	128	118
LVEDD (mm)	39.51 ± 8.11	45.89 ± 8.66[a]	48.56 ± 8.92[a,b]	48.47 ± 8.62[a,b]
IVST (mm)	9.11 ± 1.95	12.13 ± 2.21[a]	13.32 ± 2.14[a,b]	13.62 ± 2.24[a,b]
LVPWT (mm)	9.01 ± 2.14	13.65 ± 1.85[a]	13.96 ± 1.97[a,b]	14.02 ± 2.07[a,b]
IVST (g/m^2)	100.23 ± 19.85	118.65 ± 20.58[a]	131.12 ± 21.65[a,b]	132.85 ± 20.33[a,b]
Detection rate of LVH (case/%)	6 (10.00)	20 (32.26)[a]	31 (53.45)[a,b]	32 (54.24)[a,b]

[a]$P < .01$ compared with dipper group
[b]$P < .01$ compared with non-dipper group

LVH index level and detection rate of LVH in each hypertension subgroups

The data have been collected through a research study and clinical observation involving participants with different blood pressure dipping patterns. LVEDD, IVST, LVPWT, and IVST levels in dipper group was lower than those of non-dipper, extreme dipper, or anti-dipper groups (table 3). Detection rate of LVH in dipper group was also lower than those of non-dipper, extreme dipper, or anti-dipper groups (table 3). Meanwhile, LVEDD, IVST, LVPWT, and IVST levels in non-dipper group was lower than those of extreme dipper or anti-dipper group (table 3). Detection rate of LVH in non-dipper group was also lower than those of extreme dipper or anti-dipper group (table 3). However, there was no statistically significant difference between the extreme dipper group and the anti-dipper group (table 3).

According to Table 3, the dipper group exhibited lower levels of VEDD, IVST, LVPWT, and IVST compared to the non-dipper, extreme dipper, and anti-dipper groups. This suggests that individuals in the dipper group may have a relatively healthier cardiovascular status in terms of left ventricular dimensions and thickness. Furthermore, the detection rate of LVH in the dipper group was also lower than that of the non-dipper, extreme dipper, and anti-dipper groups. This implies that individuals in the dipper group may have a lower likelihood of developing LVH, which is a pathological condition associated with increased cardiovascular risk. On the other hand, the non-dipper group had lower levels of VEDD, IVST, LVPWT, and IVST compared to the extreme dipper and anti-dipper groups. This suggests that individuals in the non-dipper group may have better cardiovascular parameters than those in the extreme dipper and anti-dipper groups. Similarly, the detection rate of LVH in the non-dipper group was lower than that of the extreme dipper and anti-dipper groups. This indicates that individuals in the non-dipper group may have a lower risk of developing LVH compared to those in the extreme dipper and anti-dipper groups. Importantly, no statistically significant difference was observed between the extreme dipper group and the anti-dipper group in terms of the parameters measured (VEDD, IVST, LVPWT, and IVST) and the detection rate of LVH. This suggests that both these groups may have similar cardiovascular characteristics and risk levels.

In summary, the results from Table 3 indicate that individuals in the dipper group tend to have lower levels of left ventricular dimensions and thickness, as well as a lower risk of LVH, compared to the other groups. The non-dipper group also shows relatively favorable cardiovascular parameters and a lower risk of LVH compared to the extreme dipper and anti-dipper groups. Meanwhile, no statistically significant differences were observed between the extreme dipper and anti-dipper groups. These findings provide insights into the relationship between blood pressure dipping patterns and cardiovascular health indicators, emphasizing the potential benefits of maintaining a normal blood pressure dipping pattern.

Detection rate of myocardial ischemia and arrhythmia

Number of myocardial ischemia, arrhythmia, ventricular arrhythmia, supraventricular arrhythmia, first degree atrioventricular block, second degree atrioventricular block and ST-T segment change in dipper group was lower than those of non-dipper, extreme dipper or anti-dipper group (table 4). Number of myocardial ischemia in non-dipper group was also lower than those of extreme dipper or anti-dipper group (table 4). However, there was no statistically significant difference between the extreme dipper group and the anti-dipper group (table 4).

The results presented in table 4 show the number of various cardiovascular conditions in different groups categorized by their blood pressure dipping patterns. Specifically, the dipper group had lower numbers of myocardial ischemia, arrhythmia, ventricular arrhythmia, supraventricular arrhythmia, first degree atrioventricular block, second degree atrioventricular block, and ST-T segment changes compared to the non-dipper, extreme dipper, and anti-dipper groups. This indicates that individuals in the dipper group may have a lower prevalence of these cardiovascular conditions compared to the other groups. Similarly, the non-dipper group exhibited a lower number of myocardial ischemia compared to the extreme dipper and

Table 4. Detection Rate of Myocardial Ischemia and Arrhythmia

Item	Dipper	Non-dipper	Extreme dipper	Anti-dipper
Number of cases	122	132	128	118
Myocardial ischemia	5 (8.33)	13 (20.97)[a]	36 (62.07)[a,b]	34 (57.63)[a,b]
Arrhythmia	12 (20.00)	29 (46.77)[a]	30 (51.72)[a]	29 (49.15)[a]
Ventricular arrhythmia	3 (5.00)	6 (9.68)[a]	6 (10.34)[a]	6 (10.17)[a]
Supraventricular arrhythmia	2 (3.33)	5 (8.06)[a]	6 (10.34)[a]	6 (10.17)[a]
First degree atrioventricular block	2 (3.33)	4 (6.45)[a]	7 (12.07)[a]	7 (11.86)[a]
Second degree atrioventricular block	1 (1.67)	4 (6.45)[a]	6 (10.34)[a]	4 (6.78)[a]
ST-T segment change	3 (5.00)	9 (14.52)[a]	8 (13.79)[a]	8 (13.56)[a]

[a]$P < .01$ compared with dipper group,
[b]$P < .01$ compared with non-dipper group.

anti-dipper groups. This suggests that individuals in the non-dipper group may have a reduced risk of myocardial ischemia compared to those in the extreme dipper and anti-dipper groups. However, no statistically significant difference was found between the extreme dipper group and the anti-dipper group in terms of the number of myocardial ischemia, indicating that both groups may have similar prevalence rates of this particular cardiovascular condition.

In summary, the results from table 4 indicate that individuals in the dipper group tend to have lower numbers of various cardiovascular conditions, including myocardial ischemia, arrhythmia, and atrioventricular blocks compared to the non-dipper, extreme dipper, and anti-dipper groups. Similarly, the non-dipper group shows a lower number of myocardial ischemia compared to the extreme dipper and anti-dipper groups. These findings suggest that maintaining a normal blood pressure dipping pattern may be associated with a reduced risk of experiencing these cardiovascular conditions. However, no significant difference was observed between the extreme dipper and anti-dipper groups in terms of the number of myocardial ischemia incidences.

DISCUSSION

Hypertension is a progressive "cardiovascular syndrome" characterized by continuous increase of arterial blood pressure, which is often accompanied by other risk factors, target organ damage, or clinical diseases.[17] Among the common cardiovascular target organ damage in hypertension, left ventricular hypertrophy (LVH) is the most common due to the increased cardiac afterload caused by the persistent increase of blood pressure and cardiac compensation.[18] LVH can then develop into hypertensive heart disease, and even eventually lead to congestive heart failure.[19]

In recent years, 24h ambulatory blood pressure monitoring has attracted more and more attention. It can more comprehensively reflect the blood pressure changes of hypertension, with better repeatability, and is less disturbed by subjective factors.[20] In the monitoring of ambulatory blood pressure, it was found that if the circadian rhythm of blood pressure in patients with hypertension weakened or disappeared, it would have a related impact on the course of disease and the accompanying target organ damage in patients with hypertension.[21, 22] This paper discusses the influence of circadian rhythm of blood pressure on LVH in patients with hypertension and its mechanism. This experiment found that LVEDD, IVST, LVPWT, and IVST levels in dipper group was lower than those of non-dipper, extreme dipper, or anti-dipper group. Detection rate of LVH in dipper group was also lower than those of non-dipper, extreme dipper, or anti-dipper group.

Essential hypertension is a kind of cardiovascular syndrome with elevated systemic arterial blood pressure as the main clinical manifestation.[23] It often coexists with other cardiovascular disease risk factors, which can lead to target organ damage such as heart, brain, kidney, and even organ failure.[24] Among the common target organ damage, the compensatory LVH caused by the increased cardiac afterload due to the continuous increase of arterial blood pressure is the most common.[25] LVH can develop into hypertensive heart disease and eventually cause congestive heart failure.[26] In this study, LVEDD, IVST, LVPWT, and IVST levels in non-dipper group was lower than those of extreme dipper or anti-dipper group. Detection rate of LVH in non-dipper group was also lower than those of extreme dipper or anti-dipper group (table 2). However, there was no statistically significant difference between the extreme dipper group and the anti-dipper group.

Ambulatory blood pressure monitoring can comprehensively, objectively, and accurately reflect the blood pressure change level and blood pressure circadian rhythm in patients with hypertension, and can better evaluate the target organ damage in patients with hypertension.[27] The 24-hour blood pressure level of normal healthy people shows a physiological circadian rhythm change.[28] The blood pressure increases in the daytime and decreases at night, showing a "dipper curve" of "two peaks and one valley". This circadian rhythm change adapts to body activities and plays an important role in protecting the structure and function of blood vessels. Patients with hypertension are prone to the disruption of the circadian rhythm of blood pressure.[29] The weakening or disappearance of circadian rhythm of blood pressure can lead to an imbalance of neurohumoral regulation, activation of renin angiotensin system, impairment of endothelial function, increase of inflammatory reaction, etc., structural changes to the walls of the blood vessels, remodeling of ventricle, and a degree of damage to target organs such as heart.[30] According to the results of echocardiography and combined with Devereux formula, LVMI can predict LVH objectively, truly and accurately, which has high sensitivity and specificity.[31] In this experiment, the number of myocardial ischemia, arrhythmia, ventricular arrhythmia, supraventricular arrhythmia, first degree atrioventricular block, second degree atrioventricular block, and ST-T segment change in dipper group was lower than those of non-dipper, extreme dipper, or anti-dipper groups.

A brain natriuretic peptide first found in pig brain in 1988, was found to increase when ventricular stress increases and is related to left ventricular mass and LVH.[32] The endogenous BNP produced by the left ventricle increased significantly when the load increased.[33] The increase of BNP concentration can reflect the increase of left ventricular end diastolic pressure, which is of great value and significance in the diagnosis of cardiac

insufficiency. The study shows that the plasma BNP level of elderly hypertensive patients with LVH is significantly higher than that of hypertensive patients without LVH and normal control group.[34] The plasma BNP concentration can better reflect the LVH and left ventricular diastolic function of elderly hypertensive patients.[35] Many studies at home and abroad have found that BNP levels in hypertensive patients with LVH are significantly higher than those in patients without LVH and in normal healthy controls.[36] The study found that BNP level in LVH group was higher than that in non LVH group. BNP level was closely related to left ventricular mass and ventricular wall thickness, and the increase of BNP level was related to the degree of myocardial hypertrophy.

LVH is the most common cause of organ damage of hypertensive heart in clinic.[37] Many factors are involved in its occurrence and development: neurohumoral regulation disorder, imbalance of immune and inflammatory regulation, massive release of inflammatory cytokines, the impairment of vascular endothelial cell function, which may participate in pathological changes, such as myocardial hypertrophy, leading to ventricular hypertrophy and even dilation in patients with hypertension.[24,38,39] We found that the number of myocardial ischemia in non-dipper group was lower than those of extreme dipper or anti-dipper groups.

In summary, hypertensive patients with weakened or disappeared circadian rhythm of blood pressure have higher nighttime blood pressure levels than those with normal circadian rhythm of blood pressure, and the incidence of LVH, myocardial ischemia, and arrhythmia is higher. Therefore, in the treatment of hypertension, we should not only pay attention to 24h stable blood pressure reduction, but also take individualized treatment according to the specific condition of patients, and pay attention to restoring the circadian rhythm of blood pressure, so as to save the damage of cardiac structure and function, reduce the occurrence of cardiovascular events such as LVH, arrhythmia, and myocardial ischemia, and truly benefit patients with hypertension.

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DATA AVAILABILITY

The experimental data used to support the findings of this study are available from the corresponding author upon request.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest regarding this work.

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