Relationship between morning peak phenomenon and early renal injury
NGAL in H-type hypertension

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ABSTRACT

Purpose: To investigate the relationship between morning blood pressure surge (MBPS) and neutrophil gelatinase associated lipocalin (NGAL) in patients with H-type hypertension.

Materials and Methods: A total of 224 patients with diagnosed H-type hypertension with homocysteine (Hcy) ⩾ 10 umol/L were selected and underwent 24-hour ambulatory blood pressure monitoring (ABPM). In the morning peak group (115 cases), NGAL and serum cystatin C levels, β2-microglobulin levels were detected in each group, and general biochemical indicators were also detected.

Results: There was no significant difference in the course of hypertension, age, blood glucose, blood lipids, Hcy, BUN, Cr, and UA between the two groups (p > 0.05). CysC, β2-MG were higher than those in the nonmorning peak group, and the difference was statistically significant (p < 0.05); Pearson correlation analysis showed that NGAL was moderately and highly correlated with CysC, systolic blood pressure morning peak, β2-MG, and high (p < 0.05), low-density lipoprotein (LDL-C), and Hcy were lowly correlated (p < 0.05); multiple linear stepwise regression analysis indicated that morning peak systolic blood pressure, CysC, β2-MG, and FBG were the risk factors for NGAL.

Conclusion: The morning peak of systolic blood pressure in H-type hypertension is an important factor causing kidney injury. Paying attention to the ambulatory blood pressure monitoring and the control of morning peak blood pressure in patients with H-type hypertension, and early screening of NGAL has important clinical significance for the early prevention and treatment of renal injury in patients with H-type hypertension.

Plain Language Summary

The morning peak of blood pressure is closely related to target organ damage.
There are few studies on the relationship between morning peak phenomenon and renal damage in patients with H-type hypertension at home and abroad.
We investigated the relationship between MBPS and NGAL in H-type hypertensive patients with BUN, Cr and UA in the normal range to provide a clinical basis for early renal protection in hypertensive patients.

Introduction

Hypertension is the most important risk factor for morbidity and mortality of cardiovascular diseases, and the plasma homocysteine (Hcy) level of patients with essential hypertension ⩾ 10 umol/L is called H-type hypertension, accounting for about 80.3% of hypertension in China [1]. Zhang et al. proposed that hypertension and hyperhomocysteinemia (HHcy) have a significant synergistic effect in inducing cardiovascular disease [2]. The rise in blood pressure in the early morning hours is a normal physiological phenomenon of circadian rhythm or circadian variability, but the morning peak phenomenon, in which blood pressure rises excessively in the early morning, is harmful to the body. More studies have shown that the morning peak of blood pressure is closely related to target organ damage, and there are more studies on the close relationship between the morning peak and stroke and coronary...
heart disease in patients with H-type hypertension at home and abroad [3], while there are fewer studies on the relationship between the morning peak phenomenon and renal impairment in patients with H hypertension, and most of them are based on blood creatinine (Cr), blood urea nitrogen (BUN), serum cystatin C (CysC) and β2-microglobulin (β2-MG), uric acid (UA) as the observation index [4–6]. Neutrophil gelatinase associated lipocalin (NGAL) is the only marker of renal structural damage currently used in clinical practice, and foreign studies have shown that blood NGAL detection can diagnose the occurrence of acute kidney injury (AKI) early, assess the severity of kidney disease, and predict morbidity and mortality [7]. In this study, we investigated the relationship between MBPS and NGAL in H-type hypertensive patients with BUN, Cr and UA in the normal range to provide a clinical basis for early renal protection in hypertensive patients.

**Information and methods**

**Research subjects**

A total of 224 patients with H-type hypertension who were hospitalised in the Department of General Medicine of the Affiliated Hospital of Chengde Medical College from May 2020 to January 2021 were selected. There were 114 males and 110 females, with an age range of 40-80 years, mean age (63.77 ± 8.75), 86 cases of H-type hypertension combined with diabetes mellitus, and a duration of hypertension (10.07 ± 8.75) years. The patients were grouped according to the sleep-valley morning peak calculation method, and those with >28 mmHg were the morning peak group (n = 109) and those with ≤28 mmHg were the non-morning peak group (n = 115).

Inclusion criteria: (1) the diagnostic criteria of essential hypertension were in accordance with the European Guidelines for the Management of Hypertension 2018; (2) H-type hypertension: plasma homocysteine ≥10umol/L on the basis of essential hypertension [1]; (3) patients with BUN, Cr and UA in the normal range. Exclusion criteria: (1) severe cardiac, cerebral, hepatic and renal diseases; (2) secondary hypertension; (3) infectious diseases; (4) endocrine diseases (except diabetes); (5) autoimmune diseases; (6) malignant neoplasms; (7) a previous diagnosis of obstructive sleep apnea syndrome; (8) night shift workers; (9) taking kidney injury drugs for at least two weeks; (10) severe trauma within 6 months and history of surgery; (11) family history of psychiatric disorders.

The study protocol was approved by the Medical Ethics Committee of the Affiliated Hospital of Chengde Medical College before the study began, and the patients and their families agreed and signed an informed consent form.

**Research methods**

**General clinical information**

Patients’ age, gender, weight, height, body mass index, duration of hypertension, whether they smoked, whether they drank alcohol, whether they had diabetes, office systolic blood pressure, office diastolic blood pressure, etc. were recorded.

**Ambulatory blood pressure measurement**

Calculation of morning peak phenomenon: morning peak variation value = the average value of systolic blood pressure within 2 h after waking up - the average value of the lowest value of blood pressure at night and the total of 3 times before and after systolic blood pressure, with a difference of >28 mmHg as a sign of morning peak, and below this value as a non-morning peak phenomenon [8]. This method is also applicable to the calculation of diastolic blood pressure MBPS. Each patient wore a non-invasive portable automatic sphygmomanometer (TM2430EX, Germany), and a suitable cuff was selected and tied to the left upper arm of the study subject, and the cuff was automatically inflated once at 15 min and 30 min intervals during daytime (6:00–22:00) and night-time (22:00–6:00 the next day), respectively, and the left upper arm was kept at the same level as the heart as much as possible during automatic inflation of the cuff, and the patient should avoid strenuous avoid strenuous activities. The blood pressure values were automatically stored after continuous monitoring for 24 h. Valid readings >85% were considered acceptable, otherwise the test was repeated on the next day. At the same time, the waking hours of subjects, the 24 h mean systolic blood pressure, 24 h mean diastolic blood pressure, daytime mean systolic blood pressure, daytime mean diastolic blood pressure, night-time mean systolic blood pressure and night-time mean diastolic blood pressure were recorded in detail. The morning peak blood pressure was calculated based on the sleep-valley morning peak.

**Biochemical index determination**

The subjects included in the study were fasted for 8h, fasting cubital veins blood were drawn by a professional nurse in the morning, and biochemical indexes
were tested by the professional staff of our laboratory department using a fully automated biochemical analyzer (Japan, Hitachi 7600), which included four major blood lipids (TG, TC, HDL-C, LDL-C), renal function indexes (Cr, BUN, UA, CysC and $\beta_2$-MG), Hcy, FBG, liver function and ion.

**NGal determination**

5 mL of fasting cubital veins blood was drawn and fully anticoagulated with EDTA, centrifuged at 3000 r/min for 30 min at low speed, and then, the supernatant was stored in a refrigerator at $-80^\circ$C for storage. The blood NGAL concentration (normal value <180ng/ml) was measured centrally by immunofluorescence dry quantification method. The test kit was provided by Joinstar Biomedical Technology Co.

**Statistical methods**

The measurement data belonging to normal distribution were expressed as mean ± standard deviation ($x \pm s$), and the non-normally distributed variables were analyzed after taking the natural logarithm normalization; the t-test was used to compare the means between two groups, and the $\chi^2$ test was used to compare the count data between groups. The correlation between NGAL and each clinical index was tested by Pearson correlation test. Multiple linear stepwise regression was applied to analyze the correlation factors affecting the level of NGAL. The difference was considered statistically significant at $p < 0.05$.

**Results**

**General conditions and biochemical indices**

There was no statistically significant difference between the two groups in terms of age, gender case ratio, BMI, duration of hypertension, smoking case ratio, alcohol consumption case ratio, diabetes case ratio, TG, TC, LDL-C, HDL-C, Hcy, FBG, Cr, BUN, UA ($p > 0.05$). There was a statistically significant difference between the two groups in terms of serum NGAL, CysC, and $\beta_2$-MG levels ($p < 0.05$) (Table 1).

**Office blood pressure and 24-h ambulatory blood pressure monitoring indexes in both groups**

The MBPS of systolic blood pressure, 24-h mean systolic blood pressure, daytime mean systolic blood pressure, and night-time mean systolic blood pressure in the morning peak group were higher than those in the non-morning peak group, and the differences were statistically significant ($p < 0.05$); there were no statistical differences in office systolic blood pressure and office diastolic blood pressure between the two groups ($p > 0.05$); there was no statistically significant difference in the magnitude of diastolic MBPS, 24-h mean diastolic blood pressure, daytime mean systolic blood pressure, and night-time mean systolic blood pressure indexes when compared between the two groups ($p > 0.05$) (Table 2).

**Table 1. Comparison of general information and biochemical indices between two groups.**

| Index                  | MBPS group ($n = 109$) | Non-MBPS group ($n = 115$) | $t/\chi^2$ | $P$  |
|------------------------|------------------------|----------------------------|------------|------|
| Gender (Men/Female)    | 50/59                  | 64/51                      | 2.142      | 0.143|
| Age                    | 64.69 ± 7.87           | 62.90 ± 8.48               | 1.630      | 0.105|
| Duration of hypertension (Yaer) | 10.01 ± 8.82       | 10.13 ± 8.74               | 0.103      | 0.918|
| BMI (kg /m$^2$)        | 23.88 ± 3.54           | 23.91 ± 3.44               | 0.058      | 0.954|
| Diabetes (n, %)        | 38 (35%)               | 48 (42%)                   | 1.119      | 0.29 |
| Smoked (n, %)          | 38 (35%)               | 50 (43%)                   | 1.742      | 0.187|
| Drank alcohol (n, %)   | 21 (18%)               | 30 (26%)                   | 1.481      | 0.224|
| FBG (mmol/L)           | 6.87 ± 2.74            | 6.25 ± 2.10                | 1.901      | 0.059|
| Hcy/umol/L             | 15.12 ± 4.38           | 16.41 ± 7.95               | −1.505     | 0.134|
| TG (mmol/L)            | 1.89 ± 1.49            | 2.04 ± 1.42                | −0.774     | 0.440|
| TC (mmol/L)            | 4.18 ± 1.24            | 4.31 ± 1.09                | 0.833      | 0.406|
| HDL-C (mmol/L)         | 1.18 ± 1.35            | 1.11 ± 0.29                | 0.535      | 0.593|
| LDL-C (mmol/L)         | 2.32 ± 0.87            | 2.46 ± 0.81                | −1.288     | 0.199|
| Cr (umol/L)            | 75.55 ± 15.43          | 75.63 ± 17.19              | −0.038     | 0.970|
| UA (mmol/L)            | 313.95 ± 63.51         | 313.87 ± 64.51             | 0.009      | 0.993|
| BUN (mmol/L)           | 5.62 ± 1.21            | 5.52 ± 1.25                | 0.009      | 0.993|
| $\beta_2$-MG (mmol/L)  | 3.56 ± 1.32            | 3.20 ± 0.75                | 8.706      | 0.000|
| CysC (mmol/L)          | 1.87 ± 0.85            | 1.37 ± 0.49                | 5.36       | 0.000|
| NGAL (mmol/L)          | 236.25 ± 52.23         | 161.41 ± 41.99             | 11.78      | 0.000|

BMI: body Mass Index; FBG: fasting blood glucose; HCY: homocysteine; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; Cr: creatinine; UA: uric acid; BUN: blood urea nitrogen;  $\beta_2$-MG: $\beta_2$-microglobulin; CysC: cystatin C; NGAL: neutrophilgelatinase associated lipocalin; MBPS: morning blood pressure surge; Non-MBPS: Non-morning blood pressure surge.
Table 2. Comparison of blood pressure and ambulatory blood pressure monitoring results between the two groups in the clinic office (mmHg, x ± s).

| Monitoring index                                      | MBPS group (n = 109) | Non-MBPS group (n = 115) | t    | P    |
|-------------------------------------------------------|----------------------|--------------------------|------|------|
| Clinic office of systolic blood pressure              | 145.85 ± 11.10        | 146.04 ± 19.38           | −0.074 | 0.941|
| Clinic office of diastolic blood pressure             | 84.69 ± 11.26         | 86.48 ± 11.59            | −1.172 | 0.243|
| MBPS of systolic blood pressure                       | 34.31 ± 7.39          | 24.80 ± 8.86             | 8.708  | 0.000|
| MBPS of diastolic blood pressure                      | 15.31 ± 2.32          | 14.77 ± 2.98             | 1.528  | 0.128|
| The average of systolic blood pressure in the 24hrs    | 154.99 ± 10.69        | 147.35 ± 12.23           | 4.947  | 0.000|
| The average of systolic blood pressure in the daytime  | 159.75 ± 12.26        | 150.48 ± 14.13           | 5.235  | 0.000|
| The average of systolic blood pressure in the night-time | 149.31 ± 11.22        | 141.48 ± 13.84           | 4.637  | 0.000|
| The average of diastolic blood pressure in the 24hrs   | 88.89 ± 13.36         | 87.83 ± 12.71            | 0.611  | 0.542|
| The average of diastolic blood pressure in the daytime | 90.94 ± 13.66         | 88.49 ± 13.18            | 1.370  | 0.172|
| The average of diastolic blood pressure in the night-time | 86.79 ± 14.01         | 86.30 ± 14.14            | 0.262  | 0.793|

MBPS: morning blood pressure surge; Non-MBPS: Non-morning blood pressure surge.

Table 3. Correlation analysis of NGAL between two groups.

| Index                    | P    | R    |
|--------------------------|------|------|
| Age                      | 0.043| 0.135|
| BMI                      | 0.626| −0.033|
| HCY                      | 0.000| 0.345|
| FBG                      | 0.000| 0.334|
| TC                       | 0.000| 0.263|
| TG                       | 0.74 | −0.022|
| HDL-C                    | 0.079| −0.118|
| LDL-C                    | 0.000| 0.266|
| BUN                      | 0.732| 0.023|
| Cr                       | 0.022| 0.153|
| UA                       | 0.839| −0.014|
| β2-MG                    | 0.000| 0.759|
| CysC                     | 0.000| 0.581|
| MBPS of diastolic blood pressure | 0.162| 0.094|
| MBPS of systolic blood pressure       | 0.000| 0.516|
| Duration of hypertension    | 0.000| 0.333|
| The average of systolic blood pressure in the 24hrs | 0.000| 0.294|
| The average of diastolic blood pressure in the 24hrs | 0.286| 0.072|

BMI: body Mass Index; HCY: homocysteine; FBG: fasting blood glucose; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; BUN: blood urea nitrogen; Cr: creatinine; UA: uric acid; β2-MG: β2-microglobulin; CysC: cystatin C; MBPS: morning blood pressure surge.

Pearson correlation analysis of NGAL and each clinical index

NGAL was moderately highly correlated with CysC, systolic morning peak, and β2-MG; lowly correlated with duration of hypertension, age, Cr, 24 h systolic blood pressure, FBG, TC, LDL-C, and Hcy; and not correlated with BMI, 24 h mean diastolic blood pressure, HDL-C, TG, and morning peak diastolic blood pressure (Table 3).

Ngal multiple linear stepwise regression correlation factor analysis

Systolic morning peak, Cys-C, β2-MG, and FBG were the most significant factors affecting NGAL levels (Table 4).

Discussion

The phenomenon that blood pressure drops to a minimum at night and rises abruptly during the transition from sleep to wakefulness is called the morning peak of blood pressure [9]. Currently, the blood pressure morning peak is mostly calculated using ambulatory blood pressure monitoring sleep-valley morning peak, which is the difference between the mean systolic blood pressure for 2 h after waking up and the mean systolic blood pressure for 1 h including the lowest systolic blood pressure during the night. Turak [10] et al. found that a 10 mmHg increase in sleep-valley morning peak was associated with a significant increase in the risk of developing chronic kidney disease. A study of 377 diabetic patients followed for 6.5 years found that an increase in sleep-valley morning peak increased the risk of proteinuria 17.41-fold [11]. Traditional renal function indicators such as BUN, Cr and UA are elevated only when renal function is more severely impaired, and these indicators lack the necessary sensitivity and specificity, and biological markers for early diagnosis of renal impairment are particularly important.

The results of this study showed that CysC, β2-MG, and NGAL levels were higher in the morning peak group than in the non-morning peak group in patients with H hypertension with BUN, Cr, and UA in the normal range. CysC is a newly discovered biomarker of endogenous renal injury, which is widely used for the detection of early and acute and chronic renal failure. CysC is neither actively secreted into the small intestine nor reabsorbed into the plasma and is completely reabsorbed and catabolized by renal tubular epithelial cells after filtration. Its concentration in serum is almost entirely dependent on renal function. There is a negative correlation between serum Cys-C and glomerular filtration rate, and serum concentrations are independent of age, muscle mass, sex, and diet. Serum CysC concentrations are extremely sensitive to changes in GFR, and serum Cys-C is elevated by minor glomerular injury and varies with disease [12,13]. Measurement of serum and urine CysC is routinely used to evaluate kidney function [14].
β2-MG is a 100 amino acid protein. Under normal physiological conditions, the concentration of β2-MG in blood and urine is very low, and if the concentration increases, it may reflect impaired glomerular filtration function or increased filtration load. If the concentration of β2-MG in urine is elevated, it can reflect impaired proximal tubular reabsorption. From a pathophysiological point of view, the β2-MG may be superior to other biomarkers in terms of both prognosis and diagnosis because it reflects not only glomerular but also tubular injury [12,15,16]. This study showed that NGAL was associated with CysC and β2-MG, further validating that NGAL is consistent with existing indicators reflecting early renal impairment CysC and β2-MG. NGAL is a 25 kDa protein belonging to the lipocalin superfamily that is linked to type IV collagenase matrix metalloproteinase-9 (MMP-9) as a monomer of 25 kDa, a homodimer of 45 kDa, or as a heterodimer of 135 kDa [17]. NGAL can be used as an acute kidney injury biomarker because it is rapidly released in renal tubular injury. NGAL has good stability and resistance to proteases, making it a preferred biomarker for clinical use [18], and studies abroad have shown that NGAL has good sensitivity and specificity in predicting kidney injury.

Morning blood pressure surge (MBPS) plays an important role in target organ damage and major adverse cardiac events. The cause of increased cardiovascular outcomes in patients with exaggerated MBPS may be explained by widened in the f(QRS-T) angle that is a ventricular repolarization parameter [19]. The results of this study showed no statistically significant difference in office blood pressure between the two groups, while the 24-h, daytime, and night-time mean systolic blood pressure and MBPS of systolic blood pressure were higher in the ambulatory blood pressure MBPS group than in the non-MBPS group, suggesting that 24-hour ambulatory blood pressure monitoring can truly reflect the fluctuation and variability of blood pressure, showing strong advantages in treatment as well as evaluation of target organ damage and prognosis, and the morning peak phenomenon puts patients' blood pressure at a high load, which leads to target organ damage. This study showed that the morning peak phenomenon was closely related to NGAL levels, and morning peak systolic blood pressure was a significant factor influencing the elevation of NGAL, further verifying that morning peak systolic blood pressure can cause renal impairment. The mechanism is that the 24 h high load and blood pressure volatility caused by the morning peak phenomenon, by promoting the atherosclerotic mechanism at all levels of the kidney and damaging the endothelium of the kidney capillaries, releasing cellular and vasoactive factors, further increasing hypertension itself causes elevated renal capillary pressure, hyperfiltration, hyperperfusion and other states, weakening renal regulatory function, which leads to hemodynamic imbalance, blood redistribution, activation of renin–angiotensin–aldosterone, promotes the formation of the morning peak of blood pressure, forming a vicious circle [4,5,20].

There are some limitations. Firstly, since the sample size of this study was small and limited to our region, further evidence with larger sample size is needed. Secondly, the sleep of patients in this study was not strictly controlled, and patients may wake up intermittently at night. Thirdly, the relevant factors collected in this study are significant, and some potential relevant factors may not be paid attention to.

**Conclusion**

In conclusion, the morning peak phenomenon in patients with H hypertension is an important factor causing renal injury, and NGAL can be one of the
important indicators of early renal injury in H hypertension. In clinical work, we should pay attention to the ambulatory blood pressure monitoring and morning peak blood pressure control in patients with H-type hypertension, and pay attention to the screening of NGAL and the early prevention and treatment of hypertensive kidney injury, which can effectively reduce the occurrence of end-stage renal disease and has important clinical significance.

**Ethics approval and consent to participate**

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Affiliated Hospital of Chengde Medical College.

**Author contributions**

Chi Zhang conceived of the study, Dan-Dan Zhang, Yu-Mei Feng, Zhan-Qiang Huang and Yun-BO Xie participated in its design and coordination, Jian Zhou and Jun Li helped to draft the manuscript. All authors read and approved the final manuscript.

**Disclosure statement**

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

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**Data availability statement**

All data generated or analysed during this study are included in this published article.

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