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Relation between blood pressure variability and early renal damage in hypertensive patients

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Abstract. – OBJECTIVE: The objective of the present study was to observe the relation between blood pressure variability (BPV) and early renal damage in hypertensive patients.

PATIENTS AND METHODS: A total of 118 hypertensive patients were consecutively selected. General parameters including sex, age, duration, and grade of hypertension, antihypertensive drugs taken, smoking status, blood sugar, blood lipid level, body mass index, indexes of 24-h ambulatory blood pressure monitoring and renal function including cystatin C (CysC), serum creatinine (SCr), angiotensin II (Ang II), microalbuminuria (mALb), and urine creatinine (UCr) were measured. Glomerular filtration rate (eGFR), endogenous creatinine clearance rate (Ccr), and urine albumin/creatinine ratio (UACR) were calculated by CysC level, SCr level, and mALb and UCr level respectively. The 24-h ambulatory blood pressure monitoring indexes included 24-h mean systolic blood pressure variability (24h-SBPV), 24-h mean diastolic blood pressure variability (24h-DBPV), day mean systolic blood pressure variability (d-SBPV), day mean diastolic blood pressure variability (d-DBPV), night mean systolic blood pressure variability (n-SBPV), and night mean diastolic blood pressure variability (n-DBPV).

RESULTS: Sixty-four hypertensive patients (54.24%) were non-dipper, and the baseline data of the two groups were comparable. The 24h-SBPV, 24h-DBPV, d-DBPV, n-SBPV and SCr, eGFR, and Ccr of the two groups showed no significant differences. The d-SBPV, n-DBPV, CysC, and Ang II of the non-dipper group were significantly higher than those of the dipper group ($p<0.05$). The mALb in both groups increased and was more obvious in the non-dipper group. UACR of the non-dipper group was significantly higher than that of dipper group ($p<0.05$), while UCr showed no difference. By Pearson correlation, d-SBPV and n-DBPV correlated positively ($p<0.05$) with CysC, Ang II, mALb, and UACR.

CONCLUSIONS: BPV of hypersensitive patients, especially the d-SBPV and n-DBPV, was closely related to indexes of early renal damage including CysC, Ang II, mALb, and UACR.

Key Words:
Hypertension, Blood pressure variability, Early renal damage, Cystatin C, Angiotensin II, Microalbuminuria, Microalbuminuria/Urine creatinine.

Introduction

Blood pressure variability (BPV) is the quantification of blood pressure fluctuation in the body over a period of time. Regulation of the cardiovascular system, external environmental factors, variation of endocrine function, breathing movement, blood volume, state of motion, and autonomic nerve tension can all cause fluctuation of blood pressure[1]. Numerous studies[2] have demonstrated that BPV is closely related to target organ injury, and is an important index to evaluate the risks of hypertension. It has greater value than mean blood pressure in predicting the risks of cardiovascular events[3]. Patients with hypertension often have renal damage, especially when night blood pressure fluctuates, which can lead to increased glomerular perfusion pressure, endothelial cell damage of glomerular capillaries, increased microalbuminuria, and continuous renal damage[4]. Also, when BPV increases, sympathetic nerves are stimulated and disorder of endocrine regulation will aggravate renal injury[5]. The aim of the present study was to analyze the relation between 24-h ambulatory blood pressure and early renal damage in hypertensive patients, providing a reference for the establishment of a sensitive index for early diagnosis of renal damage.

Patients and Methods

Patients

A total of 118 patients diagnosed with hypertension were consecutively selected from January 2014 to January 2016 in our hospital.

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Patients were diagnosed according to the diagnostic standards of the *Guidelines for Prevention and Treatment of Hypertension in China of 2010*. All patients were diagnosed with primary hypertension. Patients with secondary hypertension or primary kidney diseases were excluded. Complications of hypertension included cerebral apoplexy; cardiac insufficiency; target organ damage, such as of the brain; renal arteriosclerosis; retinal artery occlusion; basic diseases including heart, liver, lung, brain, and other organ dysfunctions; pregnant or lactating women; neuropsychological diseases; severe anxious depression and incomplete medical history. The study was approved by the Ethics Committee of our hospital and informed consent from patients and their families was received.

Research Methods and Observational Indexes

The basic parameters of patients included sex, age, duration and grade of hypertension, antihypertensive drugs taken, smoking status, blood sugar, blood lipid level, and body mass index. Ambulatory blood pressure monitoring was applied for 24 h, and the indexes of renal function included cystatin C (CysC), serum creatinine (SCr), angiotensin II (Ang II), microalbuminuria (mALb), and urine creatinine (UCr). Glomerular filtration rate (eGFR) was calculated according to the level of CysC as follows: eGFR (ml/min) = 74.835 / (CysC × 1.333). The reference range for eGFR was 80-120 ml/min. The endogenous creatinine clearance rate (Ccr) was calculated according to SCr level, with the following formula: Ccr = [(140-age) × weight (kg)] / [0.818 × SCr (μmol/)]. UACR was calculated according to the level of ALb and UCr as follows: UACR = mALb / UCr. Blood pressure can be divided into dipper and non-dipper groups according to the 24-h ambulatory blood pressure monitoring indexes. Dipper showed double peaks and valleys with 24-h blood pressure rhythm, namely, increasing between 6 am and 10 am, decreasing between 2 pm and 3 pm, increasing again at 4 pm and then decreasing slowly to the lowest valley between 2 am and 3 am. For non-dipper, the night blood pressure was less than 10% lower or higher than the day blood pressure. The 24-h mean systolic blood pressure variability (24h-SBPV), 24-h mean diastolic blood pressure variability (24h-DBPV), day mean systolic blood pressure variability (d-SBPV), day mean diastolic blood pressure variability (d-DBPV), night mean systolic blood pressure variability (n-SBPV), and night mean diastolic blood pressure variability (n-DBPV) were calculated.

Serum and Urine Index Monitoring

After fasting for 8 h and liquid fasting for 4 h, 6 ml peripheral venous blood from the elbow was collected and centrifuged at 2000 g for 30 min. The serum was collected and preserved at -20°C. CysC was measured with a specific ELISA kit (Beijing Beyotime Science and Technology Ltd, China). The microplate reader was from Bio-Rad (Hercules, CA, USA). The reference range of CysC was 0.51-1.09 mg/l. A Hitachi full-automatic 7300 biochemical analysis detector (Tokyo, Japan) was used to measure SCr, mALb, and UCr. The reference range of SCr was 44-133 μmol/l, <20 mg/d for mALb, and 0.6-2.0 g/d for UCr. Ang II was measured by radioimmunoassay, with a γ-radiation immunity counter from Beijing Liuyi Factory, and a kit from Sigma (St. Louis, MO, USA). The normal range of Ang II was 28.2-52.2 pg/ml. All assays were performed according to the manufacturer's instructions.

24-h ABPM Monitoring

A noninvasive and portable ambulatory blood pressure monitoring device (Welch Allyn ABPM6100 Type, Applied Biosystems, Foster City, CA, USA) was applied. The cuff was fastened to the left arm, and the day time (8:00 am-8:00 pm) and night time (8:01 pm-7:59 am) measuring parameters were established, with a measuring frequency of once per hour during day time and once every 2 h during night time. The left arm was kept still and relaxed during normal daily activities. Patients were advised to avoid strenuous exercise and large emotional fluctuations. If patients felt discomfort or suffered from an accident, it should have been recorded immediately.

Statistical Analysis

SPSS20.0 statistical software (Version X; IBM, Armonk, NY, USA) was used for data analysis. Measurement data are presented as a mean ± standard deviation, and independent-sample *t*-test was applied for comparisons between groups. After normality test, the correlation analysis of measurement data was detected by the Pearson

Table I. Comparison of baseline parameters between the two groups.

Group	Dipper group (n=54)	Non-dipper group (n=64)	t/χ^2	p
M/F	31/23	35/29	0.088	0.767
Age (y)	56.6±9.8	57.5±8.5	0.155	0.723
Hypertension duration (m)	7.8±2.3	8.0±2.6	0.237	0.659
Hypertension grade [cases (%)]			0.017	0.992
Level I	8 (14.8)	10 (15.6)		
Level II	30 (55.6)	35 (54.7)		
Level III	16 (29.6)	19 (29.7)		
Smoking [cases (%)]	12 (22.2)	18 (28.1)	0.538	0.463
Antihypertensive drugs taken [cases (%)]	32 (59.3)	37 (57.8)	0.025	0.874
Fasting blood-glucose (mmol/l)	4.7±1.2	4.8±1.4	0.177	0.707
Total cholesterol (mmol/l)	6.6±1.4	6.7±1.6	0.102	0.846
Low Density Lipoprotein (mmol/l)	4.3±0.8	4.4±0.9	0.127	0.823
Body Mass Index (kg/m^2)	21.8±2.4	21.7±2.5	0.232	0.725

correlation. Enumeration data are presented as case or percentage (%), and comparisons between groups were by χ^2-test. $p<0.05$ was taken as statistically significant.

Results

Comparison of Baseline Parameters Between the two Groups

Sixty-four cases (54.24%) were non-dipper among the 118 patients, and the baseline parameters between the two groups were comparable (Table I).

Comparison of 24-h ABPM indexes Between the two groups

The 24h-SBPV, 24h-DBPV, d-DBPV, and n-SBPV of the two groups were compared, without any significant differences. The d-SBPV and n-DBPV of the non-dipper group were higher than those of the dipper group, and the differences were statistically significant ($p<0.05$) (Table II).

Comparison of Serum Indexes of Renal Function Between the Two Groups

SCr, eGFR, and Ccr of the two groups were compared, and there were no significant differences. CysC and Ang II of the non-dipper group were higher than those of the dipper group, and the differences were statistically significant ($p<0.05$) (Table III).

Comparison of Urinary Indexes of Renal Function Between the two Groups

The mALb in both groups increased and was more obvious in the non-dipper group. UACR in the non-dipper group was higher than that of the dipper group and the difference was statistically

Table II. Comparison of 24-h ABPM indexes between the two groups.

Group	Dipper group	Non-dipper group	t	p
24h-SBPV	14.7±3.4	14.4±3.3	0.265	0.649
24h-DBPV	6.6±1.7	6.3±1.8	0.326	0.593
d-SBPV	15.2±3.3	18.8±3.7	4.564	0.029
d-DBPV	6.2±1.4	6.4±1.2	0.393	0.547
n-SBPV	8.2±2.4	8.1±2.3	0.328	0.635
n-DBPV	6.2±1.2	9.2±1.4	4.664	0.024

Note: 24h-SBPV, 24-hour blood pressure variability; 24h-DBPV, 24-hour mean diastolic blood pressure variability; d-SBPV, day mean systolic blood pressure variability; d-DBPV, day mean diastolic blood pressure variability; n-SBPV, night mean systolic blood pressure variability; n-DBPV, night mean diastolic blood pressure variability.

Table III. Comparison of serum indexes of renal function between the two groups.

Group	Dipper group	Non-dipper group	*t*	*p*
CysC (mg/l)	0.8±0.2	3.5±1.2	5.237	0.020
Scr (μmol/L)	124.8±32.6	132.7±35.2	0.423	0.567
Ang II (pg/ml)	42.6±12.6	87.9±21.7	5.657	0.015
eGFR (ml/min)	117.3±6.4	106.5±7.2	0.235	0.862
Ccr (ml/min)	112.6±5.5	110.4±5.8	0.126	0.924

Note: CysC, cystatin C; Scr, serum creatinine; Ang II, angiotensin II; eGFR, glomerular filtration rate; Ccr, creatinine clearance rate.

Table IV. Comparison of urinary indexes of renal function between the two groups.

Group	Dipper group	Non-dipper group	*t*	*p*
mALb (mg/d)	78.5±14.6	165.4±23.7	6.237	0.010
UCr (g/d)	1.4±0.5	1.6±0.7	0.429	0.528
UACR (mg/g)	24.6±4.6	42.5±7.2	5.324	0.018

Note: mALb, microalbuminuria; UCr, urine creatinine; UACR, mALb/ UCr.

Table V. Correlation analysis of 24-h ABPM indexes and blood and urinary renal function indexes.

Indexes	d-SBPV Correlation Coefficient *r*	*p*	n-DBPV Correlation Coefficient *r*	*p*
mALb (mg/d)	78.5±14.6	165.4±23.7	6.237	0.010
UCr (g/d)	1.4±0.5	1.6±0.7	0.429	0.528
UACR (mg/g)	24.6±4.6	42.5±7.2	5.324	0.018

Note: mALb, microalbuminuria; UCr, urine creatinine; UACR, mALb/ UCr.

significant ($p<0.05$). There was no difference in the comparison of UCr (Table IV).

Correlation Analysis of 24-h ABPM Indexes and Blood and Urinary Renal Function indexes

By Pearson correlation, d-SBPV and n-DBPV were positively correlated ($p<0.05$) with CysC, Ang II, mALb, and UACR (Table V).

Discussion

Mechanism of Blood Pressure Variability in Hypertensive Patients

Apart from organ dysfunction and blood pressure level, BPV is a predictive factor for cardiovascular disease risk in hypertensive patients and is an important index of variation of microvascular resistance[6,7]. Its pathogenesis can be divided into the short-term and long-term. When the body is in a resting state, low threshold receptor values can sustainably discharge impulses, which transfer to the central nervous system by myelinated nerve fibers and regulate blood pressure at a normal level. When short-term blood pressure increases, high-threshold receptors are excited, and afferent impulses from unmyelinated fibers increase so that the baroreflex is enhanced and blood pressure decreases[8]. If autonomic nerves of the heart suffer long-term accommodative disorder, sympathetic nerve tension will increase, parasympathetic nerve tension will decrease, and blood pressure regulation will be abnormal, leading to a rise in BPV[9].

The kidney cannot excrete excessive amounts of sodium in a timely and efficient manner. Blood volume will increase, which will influence night

blood pressure so that it falls instead of rises, namely, the non-dipper or anti-dipper hypertension which manifests as increasing BPV[10]. The "morning blood pressure surge", postural hypotension, and obvious changes of long-term seasonal blood pressure in severe winters and hot summers can deteriorate the function of organs such as the heart, as well as blood vessels. The clinical treatment and prognosis are not as expected[11]. From the present study, the comparison of 24h-SBPV, 24h-DBPV, d-DBPV, and n-SBPV between the two groups showed no differences, while d-SBPV and n-DBPV of the non-dipper group were significantly higher than those of dipper group, which suggested that the abnormality of d-SBPV and n-DBPV was more closely related to hypertensive target organ damage, especially abnormal renal function.

Research on Serum Indexes of Renal Function

Glomerular filtration is achieved by a mechanical and charge-selective barrier[12]. When a part of the kidney is destroyed, the remaining kidney has the ability to compensate and reserve. Serum creatinine can be maintained within a normal range during early hypertensive renal damage and increases gradually with a progression of illness[13]. After being filtered by the glomerulus, positively charged CysC can be absorbed and degraded in the kidney tubules. Furthermore, kidney tubules do not secrete CysC[14]. One study[15] confirmed that CysC could be measured during early renal damage, and its levels rose with the extent of renal damage. It was concluded that eGFR was relatively high in hypertensive patients with early renal damage, according to CysC level[16].

The renin-angiotensin system (RAS) is an important internal regulatory mechanism that regulates kidney hemoperfusion, metabolism, and absorption of substances. Renal ischemia can stimulate RAS activity and increase Ang II secretion, resulting in continuous contraction of glomerular arterioles, which in turn causes intraglomerular pressure to rise, and filtration pressure and perfusion pressure to decrease, resulting in decreased glomerular filtration rate[17]. Furthermore, Ang II can enhance sympathetic nerve activity, and cause a chain amplification and synergistic effect, which can lead to continue development of kidney lesions[18].

This study found that SCr, eGFR, and Ccr of the two groups were not significantly different. CysC and Ang II of the non-dipper group were significantly higher than those of the dipper group, which suggested that the changes of serum CysC and Ang II could reflect early renal damage with more sensitivity.

Research on Urinary Indexes of Renal Function

At night, rising BPV causes significant damage to renal tissues. Moreover, the peripheral resistance and thickness of the glomerular basement membrane increases, leading to vascular endothelial cell damage, and increased mALb. Microalbuminuria is a sensitive marker of early renal damage. However, its ability to reflect hypertension-associated renal damage is poor, therefore any renal damage can cause increased mALb[19]. Also, the rising level is closely related to the degree of renal damage and disease prognosis[20]. The detection of mALb can be influenced by a variety of factors, such as urine volume, time, and diet, and the mALb/UCr ratio is relatively more stable, with more clinical application value[21]. The present work confirmed that mALb of both groups increased and was more evident in the non-dipper group. The UACR of the non-dipper group was significantly higher than that of the dipper group, and the comparison of UCr had no difference. These data demonstrate that mALb can reflect early renal damage, even though hypertensive patients from the dipper group also had increased mALb.

Further analysis revealed that d-SBPV and n-DBPV positively correlated with CysC, Ang II, mALb, and UACR. The 24-h ambulatory blood pressure monitoring has wide clinical application, with a guiding effect on early diagnosis, evaluation, treatment assessment, and prognosis of cardiovascular and cerebrovascular diseases[22]. Monitors can be worn conveniently, without influence on normal life and work, and accurately reflect fluctuations of blood pressure. In the present study, it was found that BPV of hypersensitive patients, especially the d-SBPV and n-DBPV, was closely related to indexes of early renal damage such as serum CysC and Ang II, urine mALb and m-Alb/Cr.

Conclusions

BPV of hypersensitive patients, especially the d-SBPV and n-DBPV, was closely related to indexes of early renal damage including CysC, Ang II, mALb, and UACR.

Conflict of interest

The authors declare no conflicts of interest.

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