THE CORRELATION OF URIC ACID, CYSTATIN C, AND BLOOD PRESSURE VARIABILITY IN PATIENTS WITH ESSENTIAL HYPERTENSION

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ABSTRACT

Objective*: To study the relationship between cystatin C (Cystatin C, Cys C), uric acid (Uric acid, UA), and blood pressure variability (Blood pressure variability, BPV) in patients with essential hypertension.*

Methods: *430 patients with essential hypertension were divided into 3 groups: grade 1 hypertension (96 patients), grade 2 hypertension (112 patients), and grade 3 hypertension (120 patients). 102 patients with normal blood pressure patients were designated as a control group. Patients' Cys C and UA were tested, and their ambulatory blood pressure was monitored for 24h. The relationships between Cys C, UA, and BPV were analyzed.*

Result: *Cys C, UA, and BPV of the grade 3 group were higher than other groups. Cys C was positively correlated with pulse pressure, 24hSSD, dSSD, and nSSD. UA was positively correlated with 24hDSD, nSSD, and nDSD.*

Conclusion: *Levels of Cys C and UA are elevated in patients with hypertension, which increases blood pressure variability. Reducing levels of Cys C and UA may effectively control blood pressure in hypertensive patients, potentially improving their prognosis, quality of life, and survival rate.*

Keywords: *Hypertension, uric acid, cystatin C, blood pressure variability.*

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Introduction

During periods of physiological and environmental stress, changes in blood pressure maintain adequate blood flow to the organs. This fluctuation in blood pressure is called blood pressure variability (BPV) and is an indicator for 24h ambulatory blood pressure monitoring. BPV can also be used as an indicator of target organ damage and informs prognosis in patients with hypertension(1). Cystatin C (Cys C) is an endogenous cysteine protease inhibitor and a risk factor for cardiovascular disease in patients with hypertension(2). In epidemiology and pathology, uric acid (UA) is closely related to hypertension and cardiovascular disease and is an independent risk factor for hypertension, acute myocardial infarction, stroke, and other cardiovascular events. Because its levels are easily controlled, UA also reduces cardiovascular and, thus, is of great value to clinical research. The purpose of this paper is to describe the relationship between Cys C, UA, and BPV in patients with hypertension and explore the impact of Cys C and UA on the prognosis of patients with hypertension.

Subjects and methods

Subjects

430 patients, newly diagnosed with essential hypertension, were admitted to our hospital's hypertension ward on their first visit between January 2013-June 2014. This group included 239 males and 191 females, aged 20-91 years (59.55±13.34). Following the Chinese Guidelines for the Prevention and

Treatment of Hypertension (2010), patients were divided into 3 groups: Grade 1 hypertension (N=96), Grade 2 hypertension (N=112), and Grade 3 hypertension (N=120) (Table 1) 102 patients with normal blood pressure were used as the control group. Patients who had secondary hypertension, had taken antihypertensive drugs, were taking drugs that affect Cys C or UA, or were diagnosed with liver or kidney dysfunction were excluded.

Grade	Systolic pressure (SBP)	Diastolic pressure (DBP)
Grade 1 hypertension	150-159	90-99
Grade 2 hypertension	160-179	100-109
Grade 3 hypertension	≥180	≥110

Table 1: Grades of hypertension (mmHg).

Methods

General Information

Basic demographic data - gender, age, disease course, smoking history, drinking history, height, weight, etc. - were collected, and body mass index (BMI) was calculated.

Biochemical examination

Fasting and water deprivation were undertaken for 12 hours prior to blood collection, and consumption of alcohol or a high purine diet was restricted. 2 mL of fasting elbow vein blood was collected from each patient. Levels of UA, Cys C, fasting blood glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (SCr), and urea nitrogen (Urea) were determined using a Beckmanau 5800 automatic biochemical analyzer.

Methods and indicators of ambulatory blood pressure monitoring

All subjects were fitted with an American Welch Allyn (Wei Lun) non-invasive, portable ABMP6100 monitor at 08:00. If a patient's blood pressure (BP) differed by >10 mmHg between their left and right sides, the cuff was fastened 2-3cm above the elbow joint of the upper arm on the side with the higher BP and, otherwise, to the left side. Patients were then advised to stretch two fingers until 08:00 the following morning. Monitoring was undertaken once every 30 minutes from 07:00-23:00, and once per hour from 23:00-07:00 the following day. Patients were advised to avoid strenuous exercise. Ideally, >80% of BP readings were accurate.

Recorded indicators included pulse pressure, heart rate, 24-hour mean systolic blood pressure (24hSBP), 24-hour mean diastolic blood pressure (24hDBP), mean daily systolic blood pressure (diurnal mean systolic blood pressure, DSBP), diurnal mean diastolic blood pressure (dDBP), nocturnal mean systolic blood pressure (nSBP), nocturnal mean diastolic blood pressure (nDBP), 24h systolic blood pressure standard deviation (24hSSD), 24-hour diastolic blood pressure standard deviation (24hDSD), diurnal systolic blood pressure standard deviation (dSSD), diurnal diastolic blood pressure standard deviation (dDSD), nocturnal systolic blood pressure standard deviation (nSSD), nocturnal diastolic blood pressure standard deviation (nDSD), et al. Standard deviation was used as an indicator to evaluate BPV.

Statistical analysis

All data were processed using SPSS17.0 statistical software. The measured data were non-normally distributed, so were expressed as medians (interquartile range), Rank comparison tests were used to compare measurements between groups. Enumeration data were expressed by cases and percentages, and comparisons between groups were tested by rank sum. The correlation analysis of Cys C, UA, and BPV was performed using Spearman rank correlation analysis. Results were assessed at the 95% significance level ($P<0.05$).

Results

Comparison of demographic data by group

There was no significant difference between any group and the demographic data ($P>0.05$) (Table 2).

Demographic data	Control (n=102)	Grade 1 hypertension (n=96)	Grade 2 hypertension (n=112)	Grade 3 hypertension (n=120)
Age (years)	55.86±10.83	57.02±11.38	57.14±11.76	59.51±11.02
Gender (male/female)	47/55	51/45	63/49	67/53
Course of disease (years)	8.96±3.13	-	8.85±2.74	9.05±3.45
BMI (kg/m^2)	25.51±2.04	24.61±2.55	25.36±3.43	25.39±3.04
Smoking history	37 (36.27)	45 (46.88)	61 (54.46)	65 (54.17)
Drinking history	24 (23.53)	42 (43.75)	45 (40.18)	53 (44.17)

Table 2: Comparison of demographic data by group ($\bar{x}\pm s$).

Comparison of Cys C and UA levels by group

Cys C and UA levels in patients with grades 1, 2, and 3 hypertension were significantly higher than those in the control group (P<0.05). Cys C and UA levels in patients with grades 2 and 3 hypertension were significantly higher than in patients with grade 1 hypertension (P<0.05) (Table 3).

Group	N	Cys C (mg/l)	UA (μmol/L)
Control	102	0.87±0.15	266.02±65.38
Grade 1 hypertension	96	0.99±0.20*	307.26±71.58*
Grade 2 hypertension	112	1.17±0.19*#	341.74±93.05*#
Grade 3 hypertension	120	1.46±0.16*#	378.12±95.96*#

Table 3: Comparison of Cys C and UA levels by group ($\bar{x}\pm s$).

Comparison of BPV indicators by group

Levels of 24hSSD, 24hDSD, and dSSD in patients with grades 1, 2, and 3 hypertension were significantly higher than those of the control group (P<0.05). Levels of 2dDSD, nSSD, and nDSD in patients with grade 3 hypertension were significantly higher than levels of grade 1 and 2 hypertension patients and controls (P<0.05) (Table 4).

Indicator (mmHg)	Control (n=102)	Grade 1 hypertension (n=96)	Grade 2 hypertension (n=112)	Grade 3 hypertension (n=120)
24hSSD	9.65±2.06	11.41±2.57*	12.32±3.10*	15.07±3.15*#△
24hDSD	7.46±1.35	8.39±2.18*	8.93±2.07*	10.35±2.61*#△
dSSD	9.20±2.04	11.13±3.05*	11.62±2.85*	14.46±3.25*#△
dDSD	7.39±1.39	8.12±2.39	8.18±2.05	9.93±2.60*#△
nSSD	9.79±2.88	10.05±3.18	11.25±3.88	12.72±4.51*#△
nDSD	7.62±2.78	8.05±2.60	8.40±3.33	9.38±3.67*

Table 4: Comparison of BPV indicators by group ($\bar{x}\pm s$). **Compared with the control group (P<0.05); #compared with the grade 1 hypertension group (P<0. 05); △compared with the grade 2 hypertension group (P<0.05).*

Cys C, UA, and BPV correlation analysis

Cys C was positively correlated with pulse pressure, 24hSSD, dSSD, and nSSD, and UA was positively correlated with 24hDSD, nSSD, and nDSD (Table 5).

Indicator (mmHg)	Cys C		UA	
	r	*P*	r	*P*
24hSSD	0.122	0.007	0.058	0.206
24hDSD	0.082	0.072	0.151	0.001
dSSD	0.108	0.017	-0.029	0.528
dDSD	-0.006	0.889	0.005	0.913
nSSD	0.131	0.004	0.186	<0.001
nDSD	0.059	0.198	0.112	0.014
Pulse pressure	0.229	<0.001	-0.084	0.065

Table 5: Cys C, UA, and BPV correlation analysis.

Ordered logistic regression

Ordered logistic regression was performed with hypertension grade as the dependent variable and UA, Cys C, etc. as independent variables. The results showed that UA and Cys C are risk factors for hypertension (Table 6).

Factor	*β*	*SE*	Wald	*P*	*OR*	95% CI
UA	1.368	0.513	7.268	0.006	3.652	1.459,10.613
Cys C	1.611	0.316	22.458	0.020	5.701	2.339,10.568

Table 6: Logistic regression analysis of risk factors affecting hypertension.

Discussion

With continuing improvement in people's living standards, increases in dietary fats and sugars, and reductions in physical activity, the population with hypertension is trending younger. As the course of the disease progresses, target organs, such as the heart and kidneys, will begin to show damage. High BPV in patients with hypertension is due to long-term pressure on the cardiovascular system, which leads to structural and functional damage to the vascular system. Previous studies have shown that the correlation between blood pressure variability and target organ damage is higher than blood pressure levels. That is, BPV is a more important contributor than BP to target organ damage[3], which may be due to the effect of increased BPV on the body fluid regulation system, which increases cardiomyocyte apoptosis, and its involvement in inflammatory responses that eventually lead to target organ damage.

Cys C is a low-molecular, secreted, non-glycosylated basic protein that is expressed in all nucleated cells. Because of its small molecular weight and positive charge, Cys C can pass freely through the glomerular filtration membrane. Because Cys C is filtered almost solely by the glomeruli, it is an ideal means of evaluating the glomerular filtration rate. Indeed, studies have shown that Cys C is more sensitive to a slight decrease in glomerular filtration rate than creatinine, especially in the elderly, because creatinine cannot truly reflect its glomerular filtration function[4]. Thus, Cys C can replace creatinine as a marker for detection of target organ damage in patients with hypertension[5]. In a study of 60 patients with essential hypertension, Watanabe et al. () found that Cys C is correlated with left ventricular myocardial weight index, arteriosclerosis, and 24-hour mean BP[6]. In patients without chronic kidney disease and hypertension, Cys C levels are high, and

renal function is slightly decreased[7]. Epidemiological studies have shown that hyperuricemia can cause vascular endothelial dysfunction, promotes the development of hypertension[8], and is an independent risk factor for hypertension[9]. Hyperuricemia may be related to vascular structural dysfunction caused by the deposition of uric acid on the blood vessel wall, increased generation of oxygen free radicals, proliferation of smooth muscle cells, activation of the renin-angiotensin system, activation of the vascular endothelial inflammatory response, insulin resistance, and other mechanisms. The Afshin study showed that decreasing UA levels causes BP to decrease in patients with hypertension[10].

This paper examined Cys C and UA levels in patients with hypertension and explored the relationship between Cys C and UA levels and BPV. The results suggest that patients with grade 3 hypertension display higher levels of Cys C, UA, and BPV. As Cys C increases, the variability of pulse pressure and systolic pressure increases; the higher the UA, the greater the 24h and nocturnal diastolic blood pressure variability and nocturnal systolic blood pressure variability. In conclusion, Cys C and UA are risk factors for hypertension. This finding indicates that levels of Cys C and UA in patients with hypertension should be monitored closely to effectively lower blood pressure, improve prognosis, and improve quality of life and survival status of patients.

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