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Original Article

Correlation study on the blood pressure variability, serum high-sensitivity C-reactive protein and homocysteine of patients with stable angina pectoris and hypertension

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Abstract: To study the correlation among blood pressure variability, serum high sensitivity C-reactive protein (hs-CRP) and homocysteine (Hcy) in patients combined with stable angina pectoris (SAP) and hypertension. A total of fifty-six patients with the isolated hypertension without any complications admitted to Wuhan No. 4 Hospital from June 2018 to June 2019 were included in the hypertension group, and at the meanwhile, 56 patients with SAP and hypertension admitted to Wuhan No. 4 Hospital during the same period were selected as complication group. The levels of Hcy and hs-CRP were detected and compared between the two groups of patients, and the blood pressure variability index was measured and calculated in the two groups of patients, in order to compare the types of blood pressure circadian rhythm in the two groups. The levels of serum hs-CRP and Hcy in the complication group were higher than those in the hypertension group, for which the difference was statistically significant ($P<0.05$). The normal rate of blood pressure circadian rhythm in the hypertension group was 62.50%, while it was 30.36% in the complication group. The circadian rhythm of blood pressure in the hypertension group was better than that in the complication group ($P<0.05$); the 24 h blood pressure level and blood pressure variability index of the complication group were higher than those of the hypertension group ($P<0.05$); the day variability indicators and night variability indicators of blood pressure in the complication group were higher than those in hypertension group ($P<0.05$); serum hs-CRP and Hcy levels were positively correlated with various blood pressure variability indicators ($r\geq0.3$, $P<0.05$). The incidence of reverse-dipper and deep-dipper blood pressure circadian rhythms was higher in SAP patients combined with hypertension, and the blood pressure variability was positively correlated with serum high-sensitivity C-reactive protein and homocysteine levels.

Keywords: Stable angina pectoris, hypertension, homocysteine, high sensitivity C-reactive protein, blood pressure variability, circadian rhythm

Introduction

Hypertension is regarded as an independent risk factor for cardiovascular and cerebrovascular diseases. There are about 14.29% on the prevalence of hypertension in China, while the prevalence of hypertension can reach about 50% for those who are over 60 years old. Nowadays, there are about 10 million new patients with hypertension every year [1-3]. The disease can induce many cardiovascular and cerebrovascular diseases, for which the combined stable angina pectoris can be commonly seen among them. Stable angina pectoris (SAP) is a kind of coronary atherosclerotic heart disease (coronary heart disease), which means that the frequency, pain degrees, nature and others of angina pectoris lasting over a period of time maintains at a relatively stable level [4-6]. SAP is mainly caused by overwork, and most of the squeezing pain can be seen in the precardiac area, which belongs to stable fatigue angina pectoris. SAP patients often combine with hypertension, while SAP and hypertension often occur together, and at the same time they are mutual risk factors. The expression of high sensitivity C-reactive protein (hs-CRP) and homocysteine (Hcy) can be abnormally elevated during the formation and evolution of hypertension combined with SAP. Blood pressure is a

Table 1. Comparison of serum hs-CRP and Hcy levels between two groups (x ± sd)

Group	n	Hcy (μmol/L)	hs-CRP (mg/L)
Hypertension Group	56	14.74±4.51	7.87±2.23
Complication Group	56	23.41±5.55	10.71±3.46
t		9.075	5.152
P		0.000	0.000

basic motive force for maintaining the blood circulation of the human body. Under the normal conditions, the level of blood pressure can have a certain degree of normal fluctuation affected by the internal steady state and external environment changes, which is so-called the blood pressure variability, and its normal state for the linear characteristic of the circadian rhythm is defined as that the dipper shape is shown. Patients with hypertension, especially those with hypertension and combined cardiovascular and cerebrovascular diseases, have the abnormal performance for the fluctuations on hypertension, as same as circadian rhythms. Therefore, the correlation analysis on the blood pressure variability, circadian rhythm and the expression levels of hs-CRP and Hcy can provide the scientific foundation for disease prediction and diagnosis on SAP, other cardiovascular and cerebrovascular systems.

Materials and methods

General information

From June 2018 to June 2019, 56 patients with isolated hypertension admitted to Wuhan No. 4 Hospital were selected and included in hypertension group. In addition, 56 patients with SAP and hypertension who were admitted to Wuhan No. 4 Hospital during the same period were included in the complication group. There were 31 males and 25 females in the hypertension group, aged 41-75 years old, with an average age as 58.65±8.32 years old; the body mass index (BMI) was 20.17-25.96 kg/m^2 and 23.13±2.61 kg/m^2 respectively. There were 30 males and 26 females in the complication group, aged 43-76 years old, with an average age as 59.13±8.69 years old; the BMI was 20.05-25.81 kg/m^2 and 23.09±2.57 kg/m^2 respectively. There was no statistical difference in the general data between the two groups (P>0.05).

Criteria for data selection

Diagnostic criteria: the relevant standards of primary hypertension on the Clinical Guidelines for Diagnosis and Treatment of Chronic Stable Angina Pectoris and Chinese Guidelines for the Management of Hypertension in the 2010 edition [7, 8]. Inclusion criteria: ① patients who met the above diagnostic criteria of SAP and primary hypertension in the complication group [9], and the patients met the above diagnostic criteria for hypertension without any history of heart, lung, liver, and kidney complications and related diseases in the hypertension group; ② patients aged >18-year-old for the first-visit in Wuhan No. 4 Hospital; ③ patient and family members who voluntarily participated and signed informed consent. This study was approved by the ethics committee of Wuhan No. 4 Hospital. Exclusion criteria: ① patients who had heart rate <60 beats/min, and the complications as atrioventricular block of II degree or over II degree, atrial fibrillation, sinus node syndrome, congenital heart disease, rheumatic heart disease and other heart diseases; ② patients who was diagnosed with malignant cancer; ③ patients who had secondary hypertension, pregnancy-induced hypertension syndrome and other types of hypertension; ④ patients who had cerebrovascular disease; ⑤ patients who had blood creatinine >1.7 mg/dl; ⑥ patients who had infectious diseases and adverse events for acute cardiovascular and cerebrovascular state in the acute phase, 7 d after surgery and 7 d after trauma; ⑦ female patients who were at the state of pregnancy and lactation; ⑧ patients who were unable to cooperate with the study for mental system diseases, cognitive dysfunction and other factors.

Observation indicators

The levels of Hcy and hs-CRP were detected and compared between the two groups. The circadian rhythm types of blood pressure were compared in the two groups, including reverse-dipper type, non-dipper type, dipper type, and over-dipper type. The blood pressure variability indicators of patients were monitored and cal-

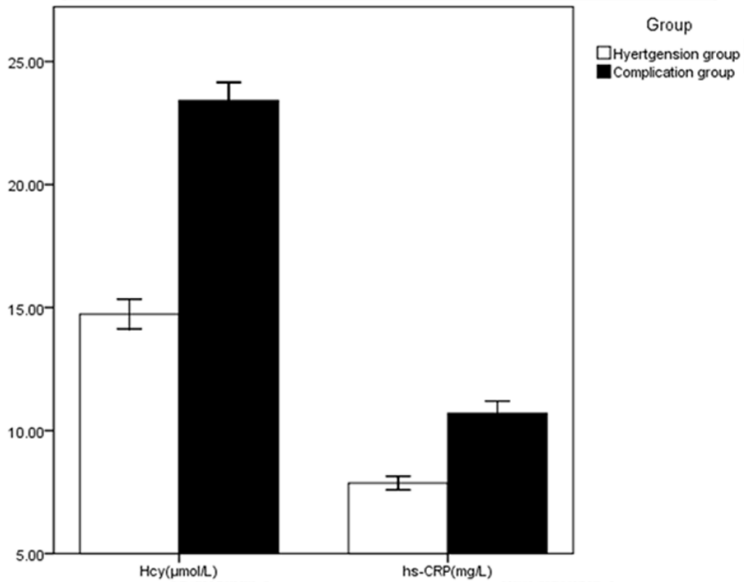

Figure 1. Comparison of the serum levels of hs-CRP and Hcy between the two groups. Compared with hypertension group, $P<0.05$.

culated in the two groups: ① 24 h observation indicators: 24 h systolic blood pressure (24hSBP), 24 h diastolic blood pressure (24hDBP), 24hSBP standard deviation (24hSSD), 24hSBP coefficient of variation (24hSCV), 24hDBP standard deviation (24hDSD), 24hDBP coefficient of variation (24hDCV); ② Daily (6:00-22:00) observation indicators: day SBP standard deviation (dSSD), day SBP coefficient of variation (dSCV), day DBP standard deviation (dDSD), day diastolic pressure coefficient of variation (dDCV); ③ Observation indicators at night (22:00-6:00): night SBP standard deviation (nSSD), night SBP coefficient of variation (nSCV), night DBP standard deviation (nDSD), night DBP coefficient of variation (nDCV). The correlation of the serum levels of hs-CRP and Hcy with blood pressure variability index was analyzed.

Observation methods

All blood pressure monitoring indexes were detected by MK-WABP portable non-invasive blood pressure monitor after diagnosis and before treatment in Wuhan No. 4 Hospital. Coefficient of variation (CV) of blood pressure was calculated based on the formula: Ambulatory blood pressure standard deviation ÷ Ambulatory blood pressure value ×100%. The circadian rhythm was calculated based on the formula: (average of day systolic blood pressure - night balanced systolic blood pressure) ÷ the average of day systolic blood pressure ×100%; classification criteria: circadian rhythm <0 was defined as reverse-dipper type, 0-10% was defined as non-dipper type, 10-20% was defined as dipper type (normal), and circadian rhythm >20% was defined as over-dipper type.

Statistical analysis

SPSS 23.0 statistical software was used as the analysis tool. The rank data were performed by rank sum test, with the data expressed as n (%); the measurement data were performed by independent t test, which was expressed as mean ± standard deviation (x ± sd); the correlations were performed with Pearson test, with the relevance criteria as $|r|\geq0.3$, for which $r>0$ was represented as a positive correlation between two variables, and $r<0$ was represented as a negative correlation between two variables. $P<0.05$ was considered as the statistical significance.

Results

Higher levels of serum hs-CRP and Hcy in the complication group

The levels of serum hs-CRP and Hcy in the complication group were higher than those in the hypertension group, and the difference was statistically significant ($P<0.05$, **Table 1** and **Figure 1**).

Better circadian rhythm of blood pressure in the hypertension group

The normal rate of blood pressure circadian rhythm was recorded as 62.50% in the hypertension group, while it was recorded as 30.36% in the complication group. The blood pressure circadian rhythm in the hypertension group was better than that in the complication group ($P<0.05$, **Table 2**).

Table 2. Comparison of blood pressure circadian rhythm between the two groups n (%)

Group	n	Reverse-dipper	Non-dipper	Dipper	Over-dipper
Hypertension Group	56	4 (7.14)	15 (26.79)	35 (62.50)	2 (3.57)
Complication Group	56	9 (16.07)	25 (44.64)	17 (30.36)	5 (8.93)
Z			-2.313		
P			0.021		

Table 3. Comparison of 24 h blood pressure and blood pressure variation indexes of patients in two groups (x ± sd)

Group	n	24hSBP (mmHg)	24hDBP (mmHg)	24hSSD (mmHg)	24hSCV (%)	24hDSD (mmHg)	24hDCV (%)
Hypertension Group	56	145.40±6.27	94.73±4.71	15.91±1.91	13.03±1.07	14.26±1.33	14.11±1.61
Complication Group	56	153.49±8.93	99.05±5.30	18.46±2.09	15.49±1.44	16.06±1.63	16.25±1.78
t		5.552	4.563	6.735	10.221	6.396	6.670
P		0.000	0.000	0.000	0.000	0.000	0.000

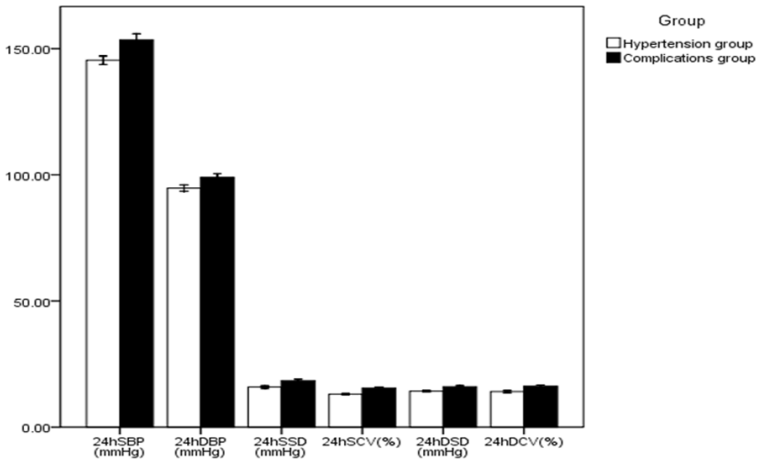

Figure 2. Comparison of serum 24hSBP, 24hDBP, 24hSSD, 24hSCV, 24hDSD and 24hDCV levels between the two groups. Compared with Hypertension group, *P*<0.05.

Higher 24 h blood pressure level and blood pressure variation index in the complication group

The 24 h blood pressure level and blood pressure variation indexes of patients in the complication group were higher than those in the hypertension group (*P*<0.05), see **Table 3** and **Figure 2**.

Higher day blood pressure variability indicators in the complication group

In the complication group, the daily blood pressure variation indexes were higher than those in the hypertension group (*P*< 0.05), see **Table 4** and **Figure 3**.

Higher night blood pressure variability indicators in the complication group

The indexes of blood pressure variability of patients in the complication group were higher than those in the hypertension group (*P*<0.05), see **Table 5** and **Figure 4**.

Positive correlation between serum hs-CRP and Hcy levels and various blood pressure variability indicators

Serum hs-CRP and Hcy levels were positively correlated with various blood pressure variability indicators (r≥0.3, *P*<0.05), as shown in **Table 6**.

Linear regression analysis

Taking whether combine stable angina or not as the dependent variable and hs-CRP and Hcy as independent variables, and since the dependent variables were nominal variables DW<2, the expression level of Hcy and hs-CRP had no effect on whether combine stable angina or not (adjusted R<60%). Anova analysis showed that differences were found between whether com-

Table 4. Comparison of the day blood pressure variation indexes between the two groups (x ± sd)

Group	n	dSSD (mmHg)	dSCV (%)	dDSD (mmHg)	dDCV (%)
Hypertension Group	56	17.13±1.37	14.45±1.08	15.22±2.16	15.34±2.86
Complication group	56	19.22±1.26	16.03±1.49	17.11±2.45	17.14±3.07
t		8.435	6.435	4.333	3.216
P		0.000	0.000	0.000	0.002

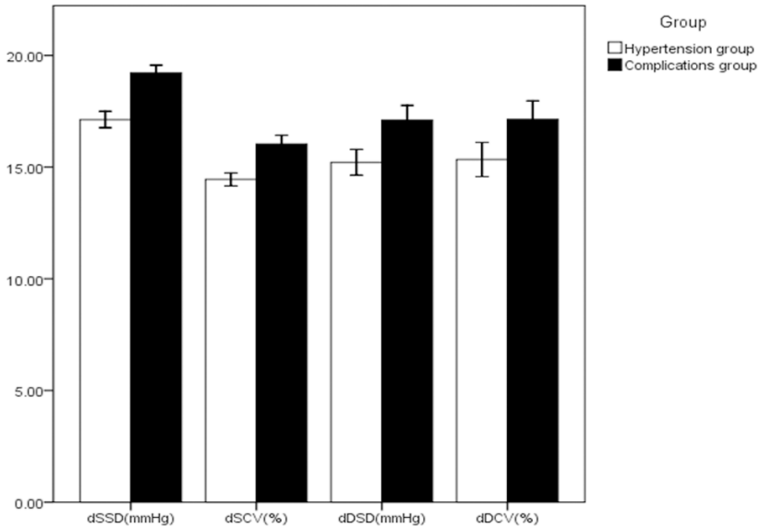

Figure 3. Comparison of serum levels of dSSD, dSCV, dDSD and dDCV between the two groups. Compared with Hypertension group, *P*<0.05.

bine stable angina or not and Hcy and hs-CRP levels (P<0.05). See **Table 7**.

Discussion

SAP is a group of clinical syndromes induced by transient myocardial ischemia and hypoxia, with the baseline disease of coronary artery stenosis. SAP can cause a transient ischemia of myocardial blood, which can trigger myocardial ischemic injury to form angina. The SAP often happens in the middle-aged population and the elderly mainly, which can lead to an increased risk of cardiovascular critical disease as the unstable angina pectoris, acute myocardial infarction and others, so that it can cause serious adverse effects on the health and life safety of patients. Hypertension is a very common clinical cardiovascular and cerebrovascular disease, which is a risk factor for SAP, as well as one of the important complications of SAP. The hs-CRP and Hcy can play important roles in the formation and progression of hypertension and SAP. As hs-CRP is an acute phase protein, which is synthesized and released into the blood under the action of inflammatory factors, it promotes the adhesion of leukocytes and its involvement in the process of atherosclerosis through endothelial tissue. The vascular endothelium of patients with SAP combined with hypertension has different degrees of damage, which triggers an inflammatory response and increases the level of hs-CRP. The formation and adhesion of atherosclerotic plaques can also form damage to the blood vessel wall and trigger an inflammatory response that leads to the increased expression of hs-CRP. When the coronary artery stenosis results in the decrease of myocardial blood supply, it can trigger myocardial tissue ischemia and hypoxic injury, so that it leads to an inflammatory response as well as significant increment in expression of hs-CRP. Therefore, patients combined with SAP and hypertension often can be seen in a micro-inflammatory state. The hs-CRP has been at a slightly high level in the serum for a long time. This state can promote the disease progression, increase the plaque instability, which can further lead to increased risk for the disease progression of patients.

Hypertensive patients with Hcy >10 μmol/L in serum are regarded as homocysteine. In clinical, there is more than 75% of hypertensive patients combined with the elevated level of Hcy [9, 10]. Along with the continuous deepening of clinical research on hypertension, homocysteine has become one of the focuses in the hypertension prevention in China. Some studies believe that with every 5 μmol/L of Hcy increases, the risk of coronary heart disease can increase by 33% [11, 12]. Homocysteine

Table 5. Comparison of day blood pressure variation indexes between two groups of patients (x ± sd)

Group	n	nSSD (mmHg)	nSCV (%)	nDSD (mmHg)	nDCV (%)
Hypertension Group	56	14.12±2.91	12.88±1.11	12.19±2.13	13.55±2.96
Complication Group	56	16.11±4.50	14.66±1.78	14.31±2.94	15.26±3.88
t		2.782	6.346	4.383	2.617
P		0.006	0.000	0.000	0.010

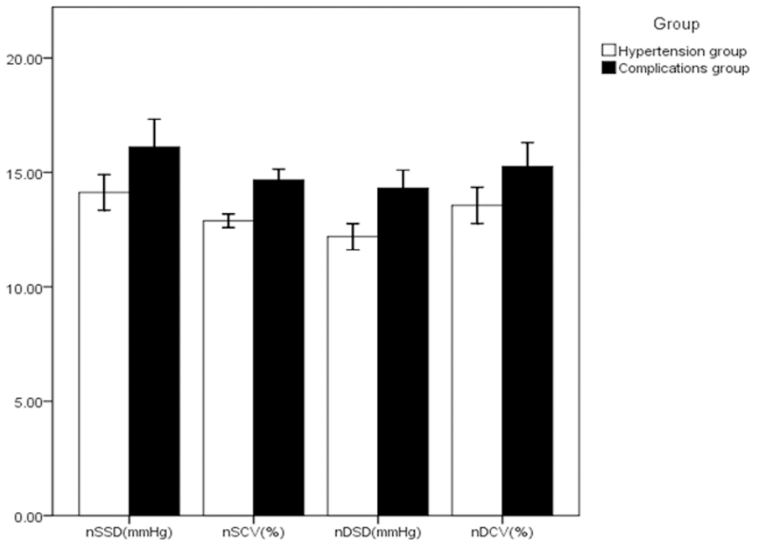

Figure 4. Comparison on the serum levels of nSSD, nSCV, nDSD and nDCV between the two groups. Compared with Hypertension group, $P<0.05$.

Table 6. Statistical values of correlation analysis on serum hs-CRP and Hcy levels with various blood pressure variability indicators

Variable	Hcy		hs-CRP	
	r	*P*	*r*	*P*
Hcy	1.000	--	0.736	0.000
hs-CRP	0.680	0.000	1.000	--
24hSBP	0.687	0.000	0.455	0.000
24hDBP	0.665	0.000	0.455	0.000
24hSSD	0.713	0.000	0.488	0.000
24hSCV	0.782	0.000	0.519	0.000
24hDSD	0.680	0.000	0.423	0.000
24hDCV	0.725	0.000	0.495	0.000
dSSD	0.747	0.000	0.497	0.000
dSCV	0.669	0.000	0.416	0.000
dDSD	0.631	0.000	0.419	0.000
dDCV	0.633	0.000	0.411	0.000
nSSD	0.582	0.000	0.368	0.000
nSCV	0.737	0.000	0.513	0.000
nDSD	0.662	0.000	0.425	0.000
nDCV	0.752	0.000	0.558	0.000

and hypertension are risk factors for SAP and other types of coronary heart disease. An additive effect can be produced when two related risk factors occur at the same time, both of them can have a complex and adverse effect on the condition of SAP, for which the mechanism is mainly related to the following viewpoints: first, the abnormal increment of Hcy can aggravate the damage degree of vascular endothelial tissue in patients with SAP and hypertension, which can result in vasoconstriction and diastolic dysfunction, further causing excessive blood pressure fluctuations and increasing blood pressure levels, so that inhibiting the decrements of Hcy metabolism-related enzyme synthesis can lead to an increased risk of SAP occurrence and progression. Second, the over-expression of Hcy can inhibit the expression of nitric oxide synthase in platelet and reduce the synthesis of nitric oxide and prostaglandin, resulting in the increment on synthesis value of arachidonic acid and thromboxane A2. Furthermore, the increased expression of adhesion molecule P-selectin can inhibit the generation of plasminogen activator in the tissue, reduce platelet activity and increase the internal adhesion of the blood, so that it could promote thrombosis. Third, the abnormal elevation of Hcy can induce coagulation disorders by forming a hypercoagulable state and promoting thrombosis. Therefore, analyzing the correlation between blood pressure variability and hs-CRP and Hcy is helpful for a more comprehensive understanding on the formation and progression of hypertension and SAP.

Table 7. Linear regression analysis between hcCRP and stable angina pectoris and hypertension and the linear regression analysis between homocysteine and stable angina pectoris and hypertension

Model	R	R-squared	Adjusted R-Square	Se	DW	F	P
Hcy	0.654	0.428	0.423	0.382	0.207	82.348	0.000
hs-CRP	0.441	0.194	0.187	0.453	0.082	26.542	0.000

Blood pressure variability is a new focus of the cardiovascular system in recent years [13]. Reducing blood pressure variability has important positive significance for preventing cardiovascular and cerebrovascular adverse events, which can prevent the occurrence of SAP or delay SAP progression [14]. The treatment of hypertension has not only focused on controlling blood pressure levels in clinic, but also reducing the risk of SAP and other coronary heart diseases by effectively controlling blood pressure variability. High blood pressure variability indicates that the fluctuation of blood pressure was overlarge in patient, which can affect the function of the vascular endothelial tissue, further cause the endothelial tissue damage and vasospasm, thereby it can continuously increase the levels of blood pressure, inducing the formation of atherosclerosis and resulting in SAP [15, 16]. At the meanwhile, the attention should also be paid on the changes in the circadian blood pressure rhythm of patients. The disorder of blood pressure circadian rhythm can cause damage to many target organs such as the cardiovascular and cerebrovascular system, kidneys and other damages to patients [17, 18]. The reverse-dipper type with a circadian rhythm <0 indicates that the blood pressure level of patients continues to rise during their rest at night, which can have an adverse effect on the hypertension and SAP of patients, and increase the risk of cardiovascular and cerebrovascular adverse events. The non-dipper type with the circadian rhythm of 0 to 10% indicates that the night blood pressure level of the patient is too low, and it is difficult for the blood vessels at all levels to relax and lay a foundation for the progression of the disease [19, 20]. The over-dipper type with a circadian rhythm >20% is likely to indicate the possibility of renal impairment. However, the kidney as another important target organ for hypertension besides cardiovascular and cerebrovascular disorders, its damage can promote the formation and progression of many lesions including SAP. Moreover, it can also increase the risk of heart failure in patients.

The results of this study showed that the levels of hs-CRP and Hcy in the complication group were higher than those in the hypertensive group, revealing that the inflammatory response of the patient was more significant when SAP and hypertension occurs together. Moreover, the risk of high-risk adverse events was higher for the higher Hcy level. The analysis on the circadian rhythm of patients between the two groups found that the normal rate of blood pressure circadian rhythm was recorded as 62.50% in the hypertension group, while it was recorded as 30.36% in the complication group. It was suggested that there was a higher risk of blood pressure circadian rhythm disorders for patients combined with SAP and hypertension, which was also one of the important causes of SAP in hypertensive patients. The blood pressure level of patients combined with SAP and hypertension could be further increased, and the blood pressure variability of patients was higher, which indicated that the blood pressure fluctuation of these patients was greater than that of patients with isolated hypertension, while the damage on the vascular endothelial tissue was more serious in the patients. Correlation analysis showed that blood pressure variability had a clear positive correlation with hs-CRP and Hcy levels, indicating that the blood pressure fluctuations of patients could increase for the increment of Hcy and hs-CRP. Furthermore, the risk of blood pressure circadian rhythm disorder and adverse events for cardiovascular system of patients was increased, so that the inflammatory stress response of body was intensified. Therefore, controlling the blood pressure variability for patients with SAP and hypertension could play a great significance for clinical treatment.

In conclusion, the blood pressure variability has a definite positive correlation with the levels of serum hs-CRP and Hcy for patients with stable angina pectoris and hypertension. Therefore, controlling the degree of inflammatory response and inhibiting homocysteine levels for pa-

tients have an important positive effect on alleviating the blood pressure fluctuation of patients and the abnormal blood pressure circadian rhythm, which can further delay the progression of stable angina pectoris and prevent the cardiovascular adverse events.

However, there are some limitations in the current study, including the small sample size of the study and many external influencing factors. Thus, sample size should be expanded, and multi-factor involvement studies should be conducted in the future.

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Disclosure of conflict of interest

None.

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