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Influence of Hypersensitive C-Reactive Protein on the Effect of Continuous Antihypertensive Pharmacological Therapy

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Abstract: Systemic chronic inflammation, represented by hypersensitive C-reactive protein (hsCRP), is an essential contributing factor to hypertension. However, the influence of hsCRP levels on the effect of antihypertensive pharmacological therapy remains unknown. We evaluated hsCRP levels in 3756 newly diagnosed, untreated hypertensive subjects. Participants were grouped by tertiles of hsCRP and were randomly treated with nitrendipine + captopril, nitrendipine + spironolactone hydrochlorothiazide + captopril, and hydrochlorothiazide + spironolactone. Blood pressure (BP) was recorded every 2 weeks. A multivariate mixed linear model was used to evaluate the impact of baseline hsCRP levels on the continuous antihypertensive effect. After 3, 6, 9, and 12 months of continuous antihypertensive treatment, no significant difference was observed in BP decline among the different hsCRP groups. We identified interactions between baseline hsCRP levels and follow-up time. After adjusting for conventional risk factors and the interactions between hsCRP and follow-up time, there was no significant association between baseline hsCRP level and antihypertensive effects at 0–6 months of follow-up. However, from 6 to 12 months, subjects with higher baseline hsCRP levels exhibited a more marked BP-lowering effect ($P < 0.001$ at 9 months, $P = 0.002$ at 12 months). Overall, there exist interaction effects between baseline hsCRP levels and follow-up time. Individuals with higher baseline hsCRP levels may exhibit a better response to antihypertensive therapy.

Key Words: antihypertensive, blood pressure, hypersensitive C-reactive protein, inflammation

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INTRODUCTION

Hypertension is the predominant, controllable risk factor for cardiovascular and cerebrovascular diseases.[1] Effective antihypertensive treatment can reduce the incidence of myocardial infarction, heart failure, stroke, and renal dysfunction.[2–5] Although the 5 major antihypertensive drug classes recommended in the current hypertension management guidelines have been associated with reduced blood pressure (BP) and cardiovascular and cerebrovascular events,[6,7] the hypertension control rate remains unsatisfactory in many areas around the world.[8] One of the reasons for this may be the lack of effective indicators to guide individualized treatment.

Chronic inflammation has been shown to be involved in the development and progression of hypertension. In the general population, increased levels of markers reflecting chronic inflammation (such as hypersensitive C-reactive protein [hsCRP], IL-6, IL-1β, IL-1Ra, and TNF-α) are associated with the development of hypertension.[9–13] In patients with chronic inflammatory diseases (such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis), the prevalence of hypertension is significantly higher than that in the population without these diseases.[14] The increase in chronic inflammatory markers is not only related to the increase in BP[9,13] but is also associated with the occurrence of target organ damage in hypertensive patients.[15,16] hsCRP is considered to be the systemic inflammatory marker with the strongest association with hypertension.[13] Therefore, we speculated that hsCRP may influence the effect of antihypertensive drugs.

Most previous studies have focused on the correlation between hsCRP and BP while very few studies have investigated the relationship between hsCRP levels and the effects of antihypertensive therapy. Mitsuyama et al [17] found that a substantial reduction in hsCRP level on antihypertensive medication may predict the benefit for cardiovascular outcomes in hypertensive women. However, that study did not analyze the impacts of baseline hsCRP levels and the effects of antihypertensive drugs. Carbone et al[18] estimated the potential influence of hsCRP on hypertension remission in hypertensive subjects with metabolic syndrome and found that low baseline hsCRP levels were associated with remission of hypertension. Although their study estimated the relationship between hsCRP and antihypertensive effects, the participants of this study all had concomitant comorbidities, that is, obesity, hyperlipidemia, and diabetes mellitus. In addition, the intervention included behavioral, dietary, and pharmacological treatments, rather than simply antihypertensive

drugs. Thus, the independent role of hsCRP in the effect of antihypertensive drug treatment is not well understood.

The Kailuan study (Trial registration number: CHICTR-TNC-11001489) is a community population-based observation and intervention study of cardiovascular diseases. In 2009, the Kailuan study performed a chronic disease management project, which offered free antihypertensive drugs for individuals identified to have hypertension in physical examinations held biennially. Therefore, this project enabled us to analyze the impact of hsCRP levels on the effects of antihypertensive drugs in hypertensive populations.

METHODS

Participants

This study was performed in the Kailuan community in Tangshan. Physical examinations were conducted every 2 years for both employed and retired employees of the Kailuan community. Eleven hospitals participated in the physical examinations. A total of 5 physical examinations were performed during 2006–2007, 2008–2009, 2010–2011, 2012–2013, and 2014–2015. From 2009, individuals with hypertension were integrated into the chronic disease management project and were provided with free antihypertensive drugs. We recruited hypertensive individuals who received antihypertensive drug therapy to participate in this study.

This study was approved by the ethics committee of the Kailuan General Hospital. Informed consent was obtained from all participants.

Inclusion and Exclusion Criteria

We included the following individuals: (1) those who completed the physical examination from 2008–2016; (2) those with systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg; (3) those who had no history of antihypertensive drug use; (4) those who had complete hsCRP measurement data; and (5) those who agreed to take antihypertensive drugs and signed the informed consent form. We excluded patients with white coat hypertension (WHC); patients with hsCRP > 10 mg/L, which may suggest acute inflammation; patients with autoimmune diseases; and patients who took antihypertensive medicine for less than 3 months.

Anthropometric Measurements

Height and body mass were measured using an adjusted RGZ-120 body mass scale (Yuanyan Co., Ltd, Jiangsu, China). Subjects were required to take off shoes and hats and to wear light clothes. The height and weight were measured accurate to 0.1 cm and 0.1 kg, respectively. Body mass index was calculated as BMI = body mass (kg)/height^2 (m^2). Smoking was defined as smoking at least 1 cigarette per day on average in the past year. Drinking was defined as drinking at least 100 mL of white wine (alcohol content >50%) per day for at least 1 year. Physical exercise was defined as performing exercise ≥3 times/wk for a duration ≥30 min/time.

hsCRP Measurement

Blood samples (5 mL) were collected from the antecubital vein between 7:00 AM and 9:00 AM after an overnight fast. Serum hsCRP levels were evaluated by immunoturbidimetry. The kit was purchased from Kanto Chemical Co., Ltd (Chuo, Japan). The reference range was 0–5 mg/L, and the minimum detectable concentration was 0.1 mg/L. Measurement of other laboratory test indexes are shown in the related literature of the Hitachi-7600 automatic biochemical analyzer (Hitachi, Chiyoda, Japan).[19] The coefficient of variation was 6.53% within the batch, 4.78% between batches, 6.61% in the daytime, and 9.37% in total, suggesting that the measurement error was small.

Office BP Measurement

BP measurements were conducted between 7:00 AM and 9:00 AM on the day of the physical examination. Smoking and drinking tea or coffee within 30 minutes before measurement were forbidden. Participants were required to sit and rest for 15 minutes. From 2006 to 2014, BP of the right brachial artery was measured using a calibrated mercury sphygmomanometer. SBP was recorded while hearing the phase I Korotkoff sounds. DBP was recorded while hearing the phase V Korotkoff sound. Three measurements were performed at intervals of 1–2 minutes. The average of 3 measurements was recorded as the final BP data. After 2014, the BP levels were measured using the HEN-8102A electronic sphygmomanometer (Omron, Dalian Co., Ltd, Dalian, China). Pulse pressure (PP) was determined as the difference between SBP and DBP. We regard the BP measured in physical examinations as office BP (OBP).

Drug Distribution Strategy

The participants were divided into 4 groups according to the last number of their physical examination IDs. If the last number of the ID was 1 or 5, patients were enrolled into group 1 and were provided with nitrendipine 5 mg twice a day (bid) + captopril 12.5 mg bid. If the last number of the ID was 2 or 6, patients were enrolled into group 2 and provided with nitrendipine 5 mg bid + spironolactone 20 mg once a day (qd). If the last number of the ID was 3, 7, or 9, patients were enrolled into group 3 and were provided with hydrochlorothiazide 12.5 mg qd + captopril 12.5 mg bid. If the last number of the ID was 4, 8, or 0, patients were enrolled into group 4 and were provided with hydrochlorothiazide 12.5 mg qd + spironolactone 20 mg qd. If the blood glucose and uric acid (UA) levels of group 3 or group 4 were higher than the normal range, patients in group 3 were provided with the same antihypertensive drugs as group 1, whereas patients in group 4 were provided with the same antihypertensive drugs as in group 2. If individuals refused to take the drugs provided above, but rather took other types of antihypertensive drugs by themselves, they were included in group 5. The selection of antihypertensive drugs was decided according to the 2009 Chinese Guidelines for the Prevention and Treatment of Hypertension. The current study was a nonblinded trial. During the 12-month follow-up on study intervention, both

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participants and investigators were aware of the type of drugs the participants used.

Follow-up and Out-of-office BP Measurement

Physical examination data were transmitted to the terminal of the community health service centers in employees' workplaces. BP measurements were performed on individuals with newly identified hypertension who were naive to antihypertensive drugs by doctors at the health service centers and were recorded as out-of-office BP. From 2006 to 2014, BP of the right brachial artery was measured using a calibrated mercury sphygmomanometer. After 2014, the BP levels were measured using the HEN-8102A electronic sphygmomanometer Omron Dalian Co., Ltd. If SBP was ≥140 mm Hg and/or DBP ≥90 mm Hg, individuals were included in the follow-up and were provided with free antihypertensive drugs. They were followed up every 2 weeks. During the follow-up, BP values, antihypertensive drug use, and adverse drug reactions were recorded.

Compliance information was obtained through questionnaires. When participants were followed up at each visit, a questionnaire was adopted to evaluate compliance, and the patients were asked to answer truthfully without concealment. The questions included the number of tablets taken, the number of tablets left at present, the reasons for not taking drugs, and whether there was any omission or withdrawal during the process of taking drugs.

Definitions and Grouping Methods

Hypertension: SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg.[6] WCH: office SBP ≥ 140 mm Hg and/or office DBP ≥ 90 mm Hg in the physical examination, but out-of-office SBP < 140 mm Hg and out-of-office DBP < 90 mm Hg.[20] Diabetes mellitus: fasting blood glucose (FBG) ≥7.0 mmol/L and/or FBG < 7.0 mmol/L with hypoglycemic drugs or a diabetic history.[21] Hyperuricemia: female UA > 357 μmol/L or male UA >416 μmol/L.[22]

Statistical Methods

The physical examination data were recorded by trained personnel at each hospital. Data were entered in the terminal of each hospital and were then uploaded to the computer room of the Kailuan General Hospital for storage in an Oracle 10.2 g database. Statistical analyses were performed using SPSS 19.0 (IBM SPSS Inc., Armonk, NY) and SAS 9.4. (SAS, Cary, NC). The baseline hsCRP values were the hsCRP values obtained at the beginning of follow-up. If the hsCRP data were missing, the missing value was replaced by the hsCRP value obtained in the previous year. We used anthropometric, biochemical, and lifestyle information of the year in which the hsCRP values were documented. Normally distributed data were recorded as mean ± SD. Analysis of variance was used for comparison between the groups. If the variance was homogeneous, the LSD test was used. If the variance was not homogeneous, Dunnett's T3 test was used. Categorical variables are described as percentages and were compared using the χ^2 test. Baseline BP and mean BP at 0–3, 3–6, 6–9, and 9–12 months after continuous antihypertensive treatment were used as dependent variables. We took the follow-up time (0, 3, 6, 9, and 12 months, with 0 months as reference), baseline hsCRP (continuous variable), and their interactions as independent variables. A multivariate mixed linear model was adopted to analyze the influence of baseline hsCRP on BP changes after continuous antihypertensive drug treatment for 3, 6, 9, and 12 months. The likelihood ratio test (LRT) was used to evaluate model fitting. Statistical significance was set at $P < 0.05$ (bilateral test) was regarded as statistically significant.

RESULTS

During 2008–2016, there were 6125 cases of hypertension (SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg) who had never taken antihypertensive drugs before. Of these, 2369 were excluded: 1711 for having WCH, 132 for lacking hsCRP data, 183 for hsCRP >10 mg/L, 74 for having autoimmune diseases, and 269 for taking antihypertensive drugs for less than 3 months. Finally, 3756 individuals were included in the statistical analysis, **Supplemental Digital Content 1** (see **Supplemental File 1**, http://links.lww.com/JCVP/A806) for the flow chart of this study.

Baseline Characteristics of Different hsCRP Groups

The mean age of participants was 47.6 ± 6.80 years, and the mean hsCRP was 1.86 ± 1.82 mg/L. We categorized participants into 3 groups according to tertiles of their hsCRP values. The first group (1252 individuals): hsCRP ≤ 0.81 mg/L; the second group (1261 individuals): 0.81 mg/L < hsCRP ≤ 1.90 mg/L; and the third group (1243 individuals): hsCRP > 1.90 mg/L. The results showed that age, BMI, total cholesterol, UA, and proportion of patients with diabetes increased with an increase in the hsCRP level. However, high-density lipoprotein cholesterol decreased with an increase in hsCRP levels. The differences between the groups were statistically significant ($P < 0.05$). Table 1 summarizes the baseline characteristics of the 3756 participants.

Antihypertensive Drug Usage and Follow-up of Different hsCRP Groups

The antihypertensive drugs used were randomized according to the last number of the patients' physical examination IDs and were then adjusted according to the blood glucose, UA, and the subjects' preferences (if they refused to take the drugs provided by this study, but rather took other types of antihypertensive drugs by themselves, they were categorized as group 5). Consequently, despite the initial randomization strategy, the adjustments of the treatment regimen during the follow-up resulted in unequal repartitioning between treatment groups. Within the 1-year follow-up, the average number of visits during 0–3, 3–6, 6–9, and 9–12 months were 5.62 ± 1.71, 4.81 ± 1.66, 4.94 ± 1.55, and 4.51 ± 1.61, respectively, and the follow-up rates were 99.9%, 92.1%, 74.4%, and 80.2%, respectively. The participants had good compliance during the follow-up and strictly followed the drug category and dosage prescribed by the investigators. We analyzed the differences in hsCRP between different treatment groups and identified no significant

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TABLE 1. Baseline Characteristics of Participants in the Different hsCRP Groups

Characteristic	Total Population (n = 3756)	The First Tertile (n = 1252)	The Second Tertile (n = 1261)	The Third Tertile (n = 1243)	F/χ^2	*P*
Age, y	47.60 ± 6.80	48.16 ± 6.72	47.72 ± 6.80*	46.89 ± 6.80*†	10.86	<0.001
Male, n (%)	3650 (97.2)	1218 (97.3)	1230 (97.5)	1202 (96.7)	3.40	0.493
HR (bpm)	77.14 ± 11.20	76.61 ± 11.54	77.11 ± 10.83	77.69 ± 11.21*	2.71	0.067
BMI (kg/m^2)	26.05 ± 3.36	25.27 ± 3.16	26.10 ± 3.22*	26.77 ± 3.51*†	62.61	<0.001
hsCRP (mg/L)	$10^{-0.09 \pm 0.98}$	$10^{-0.91 \pm 1.32}$	100.10 ± 0.10*	100.55 ± 0.19*†	1167.96	<0.001
LDL-C (mmol/L)	2.68 ± 0.78	2.63 ± 0.75	2.71 ± 0.78*	2.70 ± 0.81	3.60	0.027
FBG (mmol/L)	5.82 ± 1.63	5.76 ± 1.46	5.80 ± 1.60	5.89 ± 1.82	2.13	0.120
UA (μmol/L)	314.01 ± 100.05	303.08 ± 96.54	319.26 ± 100.34*	319.70 ± 102.40*	11.26	<0.001
Cigarette smoking, n (%)	2186 (58.9)	714 (57.9)	744 (59.6)	728 (59.1)	0.78	0.676
Alcohol consumption, n (%)	2094 (57.1)	683 (56.4)	707 (57.4)	704 (57.6)	0.41	0.814
Physical exercise, n (%)	2568 (69.9)	855 (70.4)	856 (69.3)	857 (70.1)	0.38	0.827
Diabetes mellitus, n (%)	463 (12.3)	138 (11.0)	146 (11.6)	179 (14.4)	7.57	0.023
Hyperuricemia, n (%)	579 (15.4)	153 (12.2)	222 (17.6)	204 (16.4)	15.46	<0.001

The first group (1252 individuals): hsCRP ≤ 0.81 mg/L; the second group (1261 individuals): 0.81 mg/L <hsCRP ≤ 1.90 mg/L; and the third group (1243 individuals): hsCRP >1.90 mg/L.

*$P < 0.05$ compared with the first tertile group.

†$P < 0.05$ compared with the second tertile group.

BMI, body mass index; FBG, fasting plasma glucose; HR, heart rate; hsCRP, hypersensitive C-reaction protein; LDL-C, low-density lipoprotein cholesterol; UA, urinary acid.

difference among groups. See **Supplemental Digital Content 2** (see **Supplemental File 2**, http://links.lww.com/JCVP/A807) for the detailed information about antihypertensive drug usage, follow-up frequencies, and follow-up rates of subjects in different hsCRP groups and **Supplemental Digital Content 3** (see **Supplemental File 3**, http://links.lww.com/JCVP/A808) for hsCRP levels in the different treatment groups.

Baseline BP and Antihypertensive Effects of Different hsCRP Groups

In the different hsCRP groups, although the OBP and out-of-office BP at baseline increased slightly with increasing hsCRP levels, the differences were not statistically significant ($P > 0.05$). After 3, 6, 9, and 12 months of continuous antihypertensive treatment, almost no significant difference was observed in SBP, DBP, and PP among the groups with different hsCRP levels, with the exception of DBP at 9 months, which showed a nominal difference ($P = 0.048$). Table 2 summarizes the baseline BP and effects of antihypertensive medications in the different hsCRP groups.

Influence of Follow-up Time, Baseline hsCRP, and Their Interaction on the Effect of Continuous Antihypertensive Drug Treatment

We conducted mixed linear model analyses with baseline BP and mean BP after 0–3, 3–6, 6–9, and 9–12 months' antihypertensive treatment as dependent variables and with the follow-up time, baseline hsCRP, and their interactions as independent variables. After adjusting for age, sex, heart rate, BMI, FBG, low-density lipoprotein cholesterol, UA, smoking, drinking, physical exercise, and different types of antihypertensive drugs, baseline SBP and DBP decreased by 0.38 mm Hg and 0.32 mm Hg, respectively, with each 1 mg/L increase in baseline hsCRP. There were interactions between baseline hsCRP levels and follow-up time, which influenced the antihypertensive effects of continuous drug therapy. After adjusting for these interactions, the fitting degree of the mixed linear model increased (likelihood ratio χ^2 test, $P < 0.05$).

No correlation was found between baseline hsCRP and BP decreases after 3 and 6 months of antihypertensive treatment ($P > 0.05$). However, we found significant correlations between baseline hsCRP levels and antihypertensive effects after 6 months. At 9 months, each 1 mg/L increase in baseline hsCRP was associated with a 0.41 mm Hg and 0.27 mm Hg decline in SBP and DBP, respectively ($P < 0.001$). Furthermore, after 12 months, SBP decreased by 0.38 mm Hg and DBP decreased by 0.25 mm Hg ($P = 0.002$). Table 3 summarizes the influence of follow-up time, baseline hsCRP, and their interactions on the effect of continuous antihypertensive drug therapy.

DISCUSSION

In the Kailuan cohort, we analyzed the impact of baseline hsCRP levels on the effect of antihypertensive drug treatment using a multivariate mixed linear model. Slight increases in baseline BP were observed with increasing hsCRP levels but the differences were not statistically significant. An elevated baseline hsCRP level was not significantly correlated with the antihypertensive effect at 0–6 months. However, during 6–12 months, patients with higher baseline hsCRP levels showed enhanced effects from antihypertensive treatment. Overall, individuals with higher baseline hsCRP levels may exhibit a better response to antihypertensive therapy. We found no significant difference among groups treated with different types of medication,

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TABLE 2. Baseline BP and Antihypertensive Effects in the Different hsCRP Groups

Office BP at Baseline and During Follow-up	Total Population (n = 3756)	The First Tertile (n = 1252)	The Second Tertile (n = 1261)	The Third Tertile (n = 1243)	*P*
Office BP (mm Hg)	145.74 ± 14.03	145.85 ± 13.59	145.68 ± 14.43	146.09 ± 14.05	0.123
BP before treatment (mm Hg)	144.42 ± 11.90	143.97 ± 11.12	144.32 ± 11.71	144.77 ± 12.74	0.303
SBP at the 3rd mo (mm Hg)	141.29 ± 11.21	140.58 ± 10.52	141.28 ± 10.63	141.82 ± 10.33	0.285
SBP at the 6th mo (mm Hg)	137.04 ± 11.23	136.69 ± 11.09	137.20 ± 11.25	137.03 ± 11.29	0.239
SBP at the 9th mo (mm Hg)	136.53 ± 11.87	136.49 ± 11.19	136.73 ± 11.56	136.18 ± 11.77	0.058
SBP at the 12th mo (mm Hg)	137.56 ± 12.06	137.23 ± 11.59	137.77 ± 11.97	137.46 ± 12.58	0.251
Office BP (mm Hg)	95.80 ± 8.51	95.58 ± 7.89	95.72 ± 8.67	96.09 ± 8.87	0.232
BP before treatment (mm Hg)	93.51 ± 7.34	93.27 ± 6.95	93.52 ± 7.14	94.78 ± 7.85	0.266
DBP at the 3rd mo (mm Hg)	91.17 ± 4.82	90.89 ± 4.89	91.09 ± 4.94	92.58 ± 4.63	0.423
DBP at the 6th mo (mm Hg)	88.35 ± 7.17	88.45 ± 6.95	88.52 ± 7.09	89.55 ± 7.48	0.341
DBP at the 9th mo (mm Hg)	87.70 ± 7.77	87.84 ± 7.49	87.79 ± 7.61	88.52 ± 8.17	**0.048**
DBP at the 12th mo (mm Hg)	88.03 ± 8.05	87.96 ± 7.65	88.16 ± 7.76	89.01 ± 8.71	0.336
Office BP (mm Hg)	50.14 ± 12.15	50.27 ± 12.32	50.16 ± 12.20	49.92 ± 11.78	0.243
BP before treatment (mm Hg)	51.14 ± 10.26	51.02 ± 9.92	51.19 ± 10.17	51.27 ± 10.67	0.255
PP at the 3rd mo (mm Hg)	50.35 ± 6.47	50.00 ± 6.41	50.58 ± 6.67	50.53 ± 6.33	0.261
PP at the 6th mo (mm Hg)	48.78 ± 9.48	48.56 ± 9.37	49.07 ± 9.68	48.76 ± 9.38	0.502
PP at the 9th mo (mm Hg)	49.06 ± 9.96	48.97 ± 9.90	49.33 ± 9.85	48.94 ± 10.15	0.518
PP at the 12th mo (mm Hg)	49.76 ± 10.00	49.60 ± 9.66	50.00 ± 10.10	49.73 ± 10.22	0.676

The first group (1252 individuals), hsCRP ≤0.81 mg/L; the second group (1261 individuals), 0.81 mg/L < hsCRP ≤ 1.90 mg/L; and the third group (1243 individuals), hsCRP > 1.90 mg/L.

DBP, diastolic blood pressure; hsCRP, hypersensitive C-reactive protein; Office BP, blood pressure obtained from physical examinations held every 2 years; Out-of-office BP, blood pressure obtained from community health service centers; PP, pulse pressure; SBP, systolic blood pressure.

which may suggest that the selection of different classes of drugs had no impact on hsCRP levels.

Previous studies have found that baseline SBP and DBP were higher among individuals with higher CRP levels.[11,23] The current study generally revealed a similar pattern and identified increased SBP, DBP, and PP with increasing hsCRP levels, although the differences failed to reach statistical significance.

It is well-established that traditional risk factors, particularly BMI and metabolic parameters, were correlated with hsCRP levels.[24] In the multivariate mixed linear analyses, we adjusted these factors to diminish the potential impacts. We identified interactions between baseline hsCRP levels and the duration of antihypertensive therapy on the treatment effect (*P* for interaction <0.05). We found that 6–12 months of drug therapy may result in greater BP-lowering effects among individuals with higher baseline hsCRP while no significant correlation was observed between hsCRP and the effect of antihypertensive treatment for 0–6 months.

Ridker et al[25] found that after antihypertensive drug treatment (valsartan or valsartan + hydrochlorothiazide; 1668 hypertensive patients) for 3 months, valsartan reduced hsCRP levels in a BP independent manner and the proportion of hsCRP changes explained by BP changes was <1%. In our study, during the follow-up of 0–6 months, we obtained similar results and found no significant correlation between hsCRP levels and antihypertensive effect. However, a significant association was found in patients with 6–12 months of follow-up. Thus, we believe that baseline hsCRP may exert a time-dependent influence on antihypertensive effects, and more significant BP changes may emerge with a longer follow-up. Individuals with higher baseline hsCRP levels may benefit more from antihypertensive treatment. The probable reason for the small BP changes in the current study may be the relatively short follow-up time. However, this hypothesis warrants replication in future studies with a longer follow-up duration.

Although various factors contribute to the pathogenesis of hypertension, many experimental and human studies have firmly established the role of inflammation as one of the driving forces of hypertension. Furthermore, inhibition of individual cytokines and use of immunosuppressive drugs may prevent or ameliorate experimental hypertension and reduce hypertensive organ injury.[8,26] Research has shown that elevated BP may result from the combined effects of inflammation-induced impairment in the pressure natriuresis relationship, dysfunctional vascular relaxation, and overactivity of the sympathetic nervous system.[14,27–29] Antihypertensive therapy can reduce hsCRP levels, relieve the systemic chronic inflammatory response, and thus may partly alleviate the adverse effects of inflammation on target organs.[25,30–32] However, these improvements take time. A relatively short period of treatment may not be sufficient to mitigate the effect of chronic inflammation on the human body. However, with a longer treatment duration, antihypertensive drugs may reduce chronic inflammation and facilitate BP control of high–hsCRP-mediated BP elevation.

At present, the initiation of antihypertensive treatment is predominantly dependent on BP level and cardiovascular risk assessment while systemic chronic inflammation has not

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TABLE 3. Influence of Follow-up Time, Baseline hsCRP, and Their Interactions on the Effect of Continuous Antihypertensive Drug Therapy

	Model 1		Model 2		Model 3		Model 4	
	β	*P*	B	*P*	β	*P*	β	*P*
SBP								
Follow-up for 3 mo	−3.13	<0.001	−3.13	<0.001	−3.26	<0.001	−3.40	<0.001
Follow-up for 6 mo	−7.22	<0.001	−7.21	<0.001	−7.10	<0.001	−7.41	<0.001
Follow-up for 9 mo	−7.45	<0.001	−7.45	<0.001	−6.76	<0.001	−7.11	<0.001
Follow-up for 12 mo	−6.58	<0.001	−6.58	<0.001	−5.95	<0.001	−6.26	<0.001
Baseline hsCRP			0.37	<0.001	0.49	<0.001	0.38	<0.001
hsCRP × 3-mo follow-up					0.07	0.287	0.07	0.336
hsCRP × 6-mo follow-up					−0.06	0.575	−0.09	0.411
hsCRP × 9-mo follow-up					−0.37	<0.001	−0.41	<0.001
hsCRP × 12-mo follow-up					−0.33	0.003	−0.38	0.002
Wald test for follow-up time		<0.001		<0.001		<0.001		<0.001
Wald test for hsCRP × follow-up time						<0.001		<0.001
LRT vs. model 1				<0.005		<0.005		<0.001
LRT vs. model 2						<0.005		<0.001
LRT vs. model 3								<0.001
DBP								
Follow-up for 3 mo	−2.34	<0.001	−2.34	<0.001	−2.37	<0.001	−2.50	<0.001
Follow-up for 6 mo	−4.80	<0.001	−4.80	<0.001	−4.67	<0.001	−4.90	<0.001
Follow-up for 9 mo	−5.33	<0.001	−5.33	<0.001	−4.89	<0.001	−5.17	<0.001
Follow-up for 12 mo	−5.19	<0.001	−5.19	<0.001	−4.78	<0.001	−5.12	<0.001
Baseline hsCRP			0.25	<0.001	0.35	<0.001	0.32	<0.001
hsCRP × 3-mo follow-up					0.01	0.735	0.01	0.885
hsCRP × 6-mo follow-up					−0.07	0.274	−0.11	0.114
hsCRP × 9-mo follow-up					−0.24	<0.001	−0.27	<0.001
hsCRP × 12-mo follow-up					−0.22	0.003	−0.25	0.002
Wald test for follow-up time		<0.001		<0.001		<0.001		<0.001
Wald test for hsCRP × follow-up time						<0.001		<0.001
LRT vs. model 1				<0.005		<0.005		<0.001
LRT vs. model 2						>0.250		<0.001
LRT vs. model 3								<0.001
PP								
Follow-up for 3 mo	−0.79	<0.001	−0.79	<0.001	−0.89	<0.001	−0.89	<0.001
Follow-up for 6 mo	−2.41	<0.001	−2.41	<0.001	−2.44	<0.001	−2.50	<0.001
Follow-up for 9 mo	−2.13	<0.001	−2.13	<0.001	−1.88	<0.001	−1.92	<0.001
Follow-up for 12 mo	−1.37	<0.001	−1.37	<0.001	−1.15	<0.001	−1.12	<0.001
Baseline hsCRP			0.11	0.059	0.15	0.105	0.06	0.530
hsCRP × 3-mo follow-up					0.05	0.349	0.06	0.326
hsCRP × 6-mo follow-up					0.01	0.877	0.02	0.809
hsCRP × 9-mo follow-up					−0.13	0.148	−0.13	0.176
hsCRP × 12-mo follow-up					−0.12	0.203	−0.14	0.173
Wald test for follow-up time		<0.001		<0.001		<0.001		<0.001
Wald test for hsCRP × follow-up time						0.027		0.021
LRT vs. model 1				>0.750		>0.250		<0.001
LRT vs. model 2						>0.250		<0.001
LRT vs. model 3								<0.001

Model 1, multivariate mixed linear analyses with baseline BP and mean BP of 0–3, 3–6, 6–9, and 9–12 months after continuous antihypertensive treatment as dependent variables. We took the follow-up time (0, 3, 6, 9, and 12 months, with 0 month as reference), baseline hsCRP, and their interactions as independent variables; model 2, added baseline hsCRP to independent variables on the basis of model 1; model 3, added baseline hsCRP × follow-up time to independent variables on the basis of model 2; model 4, adjusted for age, sex, HR, BMI, FBG, LDL-C, UA, cigarette smoking, alcohol consumption, physical exercise, and types of antihypertensive drugs on the basis of model 3.

DBP, diastolic blood pressure; hsCRP, hypersensitive C-reactive protein; LRT, likelihood ratio test; PP, pulse pressure; SBP, systolic blood pressure.

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been regarded as an indicator for the initiation of antihypertensive drug treatment. There is a lack of predictors for the efficiency of antihypertensive treatment. In this study, we analyzed the influence of hsCRP on the antihypertensive effect of different treatment durations and identified a positive relationship between baseline hsCRP levels and antihypertensive drug efficacy. For individuals with high baseline hsCRP levels, better BP control may be achieved by continuous antihypertensive therapy. These findings may contribute to the individualized treatment of hypertension.

WCH is a condition in which OBP is elevated while out-of-office BP is normal.[33] The prevalence of WCH was approximately 28% in the current study; however, the percentage was reported to range between 10% and 15% in previous studies. We speculate that this may be due to the BP measurement approach used in this study. Because electronic sphygmomanometers were not widely used in China before 2014, we used mercury sphygmomanometers to measure BP from 2006 to 2014, and electronic sphygmomanometers were used to measure BP after 2014. Inconsistencies in BP measurement approaches may lead to potential bias. In addition, the average of 3 consecutive BP measurements was taken as the OBP; however, some studies suggested that 5 measurements should be performed electronically, where possible, with the first and second values being ignored.[34] Therefore, the BP measurement approach and relatively few measurements may have led to an increased prevalence of WCH.

This study had some limitations. First, most participants were male, which may have resulted in a sex bias. Second, different treatment regimens were adopted in the current study, which may be a confounder for the assessment of the expected outcome. Third, this study was an unblinded study, which have may have led to bias. Fourth, the BP measurement was conducted with different methodology at baseline and follow-up, which may be a limitation in data interpretation.

CONCLUSIONS

There exist interaction effects between baseline hsCRP levels and follow-up time. Individuals with higher baseline hsCRP levels may exhibit a better response to antihypertensive therapy.

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