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Plasma Aldosterone Concentration Is Positively Associated With Pulse Pressure in Patients With Primary Hypertension

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Abstract: Increasing evidence showed a link between arterial elasticity and stiffness and pulse pressure (PP), in which plasma aldosterone may play a role. The observational study aimed to explore the potential relations between plasma aldosterone concentration (PAC) and PP in patients with hypertension.

We evaluated the relation between PP and PAC in supine, seated, and upright positions in 195 patients with primary hypertension who underwent postural stimulation test. They were divided into 3 groups by tertiles of PP: PP $\leq$ 44 mm Hg (n = 70), 44 mm Hg < PP $\leq$ 51 mm Hg (n = 63), and PP $\geq$ 51 mm Hg (n = 62). The PAC in different postures was compared, respectively.

The results showed the following. First, segregated by tertiles of PP, serum K^+, 24-hour systolic blood pressure, 24-hour diastolic blood pressure, sex, upright PAC, and seated PAC showed statistically significant differences in groups. Second, the PAC were significantly different in 3 levels of PP regardless of postures, the individuals with PP $\geq$ 51 mm Hg had the highest PAC. On contrast, the patients with PAC > 12 ng/dL showed greater PP than those with PAC $\leq$ 12 ng/dL. Third, weak associations between PP and upright ($r = 0.288$, $P < 0.001$), seated ($r = 0.265$, $P < 0.001$), and supine postures ($r = 0.191$, $P = 0.008$) were detected by simple correlation analysis. After corrected serum K^+, age, and sex, the partial correlation coefficients did not change greatly. Fourth, the logistic regression model was constructed with PP $\geq$ 40 mm Hg or PP < 40 mm Hg as the dependent variable; the serum K^+[OR = 0.043, 95% CI: 1.09(1.00–1.12)] and PAC [OR = 0.025, 95%CI: 0.35(0.13–0.88)] were included as significant contributing factors.

The results showed that higher PAC was weakly, but significantly, correlated to greater PP regardless of different postures, suggesting that higher PAC may be a risk factor of reduced arterial elasticity in patients with hypertension.

Editor: Anastasios Lymperopoulos.
Received: September 2, 2014; revised: February 10, 2015; accepted: February 11, 2015.
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This study was supported by the Special Project of Scientific and Technological Achievements Conversion of Xinjiang Uygur autonomous region (201154126).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000614

(*Medicine* 94(10):e614)

Abbreviations: 24-hr ABPM = 24-hour ambulatory blood pressure monitoring, ANOVA = analysis of variance, ARR = aldosterone to renin ratio, BMI = body mass index, BP = blood pressure, Glu = glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PAC = plasma aldosterone concentration, PP = pulse pressure, PRA = plasma aldosterone and renin activity, PST = postural stimulation test, TC = total cholesterol, TG = triglycerides.

INTRODUCTION

Increasing studies supported the association between the stiffness of the conduit vessels and cardiovascular morbidity, such as myocardial infarction,[1,2] stroke,[3] as well as left ventricular hypertrophy[4] were demonstrated to be related to aortic stiffness in both normotensive and hypertensive populations.

Aldosterone is a steroid with mineralocorticoid activity, whose classical target is the distal convoluted tubule of the kidney, and it can increase the reabsorption of sodium and excretion of potassium, and thus regulate body fluid balance. Therefore, aldosterone is widely thought to be 1 important factor of blood pressure and cardiovascular disorders; in addition to this, it could not only alter vessels' adrenergic response, but also increase arterial stiffness. Moreover, overexcretion aldosterone could advance the fibrosis of heart and vascular vessels, leading to the reduction of arterial elasticity and compliance, which was demonstrated as risk factors of aortic stiffness in early studies.[5–8] Moreover, the increase volume loading and reduced arterial elasticity would result in elevation of pulse pressure (PP). In addition, in our previous studies, the high level of plasma aldosterone was found to be positively associated with carotid atherosclerosis and ventricular structure damage in patients with hypertension.[9,10]

PP is reported to be positively correlated with aortic stiffening[4]; furthermore, increased PP has been implicated in the development and progression of large-vessel atherosclerosis[11] and small-vessel disease.[12–14] In other words, increased PP not only indicates the presence of atherosclerosis, but also indicates the poor arterial wall elasticity. PP is influenced by several cardiac and vascular factors. Commonly, the aging, aortic insufficiency, hypertension, arterial stiffness, hyperthyroidism, and acute heart failure are reasons for elevated PP level. Therefore, the PP in patients with hypertension is thought to better reflect the true state of the arterial wall; the concern of the PP would be beneficial for cardiovascular disease risk assessment and prevention.

Taking above evidence together, it is supposed that higher plasma aldosterone concentration (PAC) may be a potential risk factor for higher PP by increasing arterial fibrosis and reducing

arterial elasticity. The aim of this study was to elucidate the effect of PAC on arterial elasticity and compliance by exploring the association between PAC and PP in patients with hypertension, and to provide more information for better treatment of hypertension.

SUBJECTS AND METHODS

Initially, 317 inpatients who attended the Center of Diagnosis, Treatment and Research of Hypertension in Xinjiang of China from 2008 to 2010 were enrolled, who met one of the following criteria: first, systolic blood pressure (BP) was $\geq$140 mm Hg and (or) diastolic BP $\geq$ 90 mm Hg after cotreatment with 2 kinds of antihypertensive medications for at least 2 weeks; second, new-onset hypertension without any antihypertensive treatment.

All patients were collected for general information (eg, age, cigarette smoking, alcohol intake, etc.) and asked to undergo postural stimulation test (PST) and 24-hour ambulatory blood pressure monitoring (24-hr ABPM) simultaneously. The patients were asked to withdraw any diuretic treatments (mineralocorticoid antagonists included) for at least 6 weeks or dihydropyridine calcium blockers, β-adrenergic receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, α methyldopamine, clonidine, and nonsteroidal antiinflammatory drugs for 4 weeks before the PST. In addition, the hypokalemia were corrected to normal level before PST. When needed, the patients were allowed to continue regimens of verapamil (slow-release) and doxazosin mesylate/terazosin hydrochloride to control high blood pressure.

Patients with hyperthyroidism(n = 6), aortic insufficiency (n = 2), hypertensive heart disease (n = 8), rheumatic heart disease (n = 1), serious peripheral arterial disease (n = 2), diabetic retinopathy (n = 4), isolated systolic hypertension (n = 11), or complications of the heart, cerebrum, or kidney (n = 46), Cushing syndrome (n = 2), pheochromocytoma (n = 1), and renal artery stenosis (n = 7) were excluded, considering that some patients may present as secondary hyperaldosteronism. In addition, first, the individuals who did not complete the PAC measurement or ABPM successfully (n = 4), second, patients whose blood pressure could not be controlled lower than 160/100 mm Hg by nondihydropyridine calcium antagonists or α-blocker were also excluded (n = 28). Finally, 195 patients were involved in the present study, they were divided into 3 groups on the basis of the tertiles of 24-hour PP: lower tertile group (PP $\leq$ 44 mm Hg, n = 70), middle tertile group (44 mm Hg < PP $\leq$ 51 mm Hg, n = 63), and upper tertile group (PP > 51 mm Hg, n = 62).

The study was approved by the Ethics Committee of the People's Hospital, Xinjiang, and an informed written consent was obtained from all participants. All studies that involve the use of humans adhere to the principles of the Declaration of Helsinki.

Postural Stimulation Test

The PST was based on measurements of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) at 10:00-hour local time after 2-hour ambulation, then at midmorning after 2-hour sitting (12:00 h), and finally, at noon after 2-hour recumbency (14:00 h). The PAC in 3 postures was individually recorded as upright, seated, and supine PAC in the present study. The means of 24-hour ABPM data and mercury sphygmomanometer readings during PST were used for PP calculation.

Plasma Aldosterone Concentration and Plasma Renin Activity Measurement

As described in our previous study,[15] the blood samples were immediately centrifuged at 4°C and stored at −20°C until processed. PRA was measured by an iodine [^{125}I] angiotensin I radioimmunoassay kit & iodine [^{125}I] angiotensin II radioimmunoassay kit (Northern Biotechnology Institutes, Beijing, China), and the intra- and interassay coefficients of variation were 10% and 15%, respectively. Plasma aldosterone was measured in a blind manner by a specially assigned person in the laboratory of the Hypertension Institute, using a highly sensitive and specific radioimmunoassay (Quest Diagnostics, Madison, NJ) with a sensitivity of less than 1 ng/dL (28 pmol/L).[16] The intra- and interassay coefficients of variation were 4.5% and 9.8%, respectively. The same batches of reagents were used for all samples.

24-Hour Ambulatory Blood Pressure Monitoring

24-hr ABPM was obtained using the SpaceLabs 90207 automated noninvasive oscillometric device (SpaceLabs Healthcare, Snoqualmie, WA), programmed to register BP at 15-min intervals for the daytime (from 8:00 to 23:00, local time) and 30-min intervals for the nighttime(from 23:00 to 8:00 in the next morning, local time). The first 2 readings were omitted as they might result in inaccurate values from alerting reaction. Valid registries had to fulfill a series of preestablished criteria, including at least 80% successful recordings of both systolic and diastolic BP (SBP and DBP, respectively) during the daytime and nighttime periods, 24-hour duration and at least 1 BP measurement per hour.[17] The nondominant arm was used for cuff placement. Patients were instructed to keep their arm immobile during cuff inflation and deflation, but to otherwise go about their daily activities as planned. Taking shower, strenuous exercises, sexual intercourse, and caffeine intake were not allowed.

Biochemical Measurement

Fasting venous blood was collected to measure total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, plasma sodium, potassium, and creatinine levels were measured with an auto analyzer in the Test Center of People's Hospital of Xinjiang Autonomous Region (Tertiary Hospital).

Statistical Analysis

Data were recorded by bi-input with Epidata 3.0 after being carefully checked. Data were expressed as mean ± SD or as a median and quartile if the variables were not normally distributed. One-way analysis of variance (ANOVA) followed by post hoc test or nonparametric test was used to compare means of variables in groups. Multifactor ANOVA analysis was used to evaluate the relation between baseline PP tertile and PAC in upright, seated, and supine postures. Logistic regression models were constructed to identify variables associated with higher PP, with an inclusion and exclusion level for individual variables of 0.05 and 0.10, respectively. Statistical Package for the Social Sciences (SPSS, version 15.0) was used for all of the analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Baseline Characteristics

The baseline characteristics of the patients when segregated by tertiles of PP were displayed in Table 1. The serum K^+

TABLE 1. Characteristics of the Study Population When Segregated by Tertiles of Pulse Pressure

Variables	PP ≤ 44 mm Hg (n = 70)	44 mm Hg < PP ≤ 51 mm Hg (n = 63)	PP > 51 mm Hg (n = 62)	*P*
Age, y	42.7 ± 8.6	45.1 ± 8.4	42.8 ± 12.8	0.309
Sex (male/female)	25/45	28/35	42/20	0.001
Plasma Na^+, mmol/L	141.8 ± 2.2	141.1 ± 1.6	141.4 ± 1.7	0.082
Plasma K^+, mmol/L	4.0 ± 0.3	3.9 ± 0.4	3.8 ± 0.4	0.012
BMI, kg/m^2	25.5 ± 3.2	27.0 ± 4.1	26.1 ± 3.4	0.056
Serum creatinine, mmol/L	69.8 ± 18.0	67.7 ± 21.0	78.3 ± 43.1	0.108
Fasting Glu, mmol/L	4.8 ± 0.7	4.8 ± 0.6	4.9 ± 0.8	0.877
TC, mmol/L	4.6 ± 0.9	4.4 ± 0.7	4.5 ± 0.9	0.385
TG, mmol/L	1.6 (1.1, 2.6)	1.6 (1.1, 2.5)	1.9 (1.3, 2.8)	0.189
HDL, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	0.086
LDL, mmol/L	2.6 ± 0.6	2.4 ± 0.6	2.5 ± 0.8	0.454
Mean of 24-hr SBP (mm Hg)	126.2 ± 10.2	138.8 ± 11.7	151.9 ± 15.4	<0.001
Mean of 24-hr DBP (mm Hg)	86.6 ± 9.1	90.9 ± 11.6	93.5 ± 12.9	0.002
Current smoking (%)	33 (47.1)	20 (31.7)	23 (37.1)	0.179
Current drinking (%)	38 (54.3)	24 (38.1)	25 (40.3)	0.123
Hypertension history, y	1.0 (0.1, 5.0)	2.0 (0.0, 6.0)	2.5 (0.5, 5.0)	0.487
Upright PRA, ng/mL/h	2.9 (0.9, 4.5)	2.0 (0.8, 3.7)	2.9 (1.3, 6.6)	0.066
Upright PAC, ng/dL	14.7 (10.8, 19.9)	14.5 (9.6, 20.0)	19.1 (13.0, 28.3)	0.002
Upright ARR	5.0 (7.4)	6.7 (7.9)	5.8 (9.7)	0.187
Seated PRA, ng/mL/h	2.1 (1.0, 3.8)	1.3 (0.6, 3.0)	2.5 (0.8, 4.7)	0.082
Seated PAC, ng/dL	9.5 (6.8, 12.7)	10.5 (7.7, 16.3)	12.3 (7.7, 19.7)	0.037
Seated ARR	4.4 (5.8)	8.4 (7.5)	5.2 (9.9)	0.042
Supine PRA, ng/mL/h	1.1 (0.4, 1.9)	0.7 (0.3, 1.7)	1.2 (0.4, 2.7)	0.198
Supine PAC, ng/dL	5.4 (3.9 ± 6.8)	6.0 (4.0,9.1)	6.7 (4.2,8.7)	0.128
Supine ARR	4.9 (7.3)	8.3 (12.7)	5.5 (10.8)	0.234

24-hr DBP = 24-hour diastolic blood pressure, 24-hr SBP = 24-hour systolic blood pressure, BMI = body mass index, GLU = glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PAC = plasma aldosterone concentration, PRA = plasma renin activity, TC = total cholesterol, TG = total triglycerides, yr = year.

concentration, 24-hr SBP, 24-hr DBP, upright PAC, and seated PAC in 3 groups were significantly different, but the age, sex, BMI, serum creatinine, plasma renin activity, and supine PAC in 3 groups were not found statistically different (Table 1).

Relation Between Mean PP Tertile and PAC in Upright, Seated, and Supine Postures

Multifactor ANOVA analysis showed that PAC was significantly different in 3 levels of PP in any postures (Table 2). The means of PAC was highest in individuals with PP > 51 mm Hg (Figure 1), adjusted for age, sex, and BMI. Correspondingly, the patients with higher seated PAC (PAC > 12 ng/dL) presented greater PP level than those with lower PAC (PAC ≤ 12 ng/dL) regardless of postures (Table 3).

Correlation Analysis of PP and PAC

The simple correlation analysis showed weak association between PP and PAC in upright ($r = 0.288$, $P < 0.001$), seated ($r = 0.265$, $P < 0.001$), and supine postures ($r = 0.191$, $P = 0.008$), respectively. After adjusted for plasma potassium, age, and sex, the partial correlation coefficients (r') between PP and PAC did not change greatly, which were 0.235 ($P = 0.001$) for upright, 0.220 ($P = 0.002$) for seated, and 0.166 ($P = 0.021$) for supine, respectively (Figure 2).

Binary Logistic Regression Analysis for Pulse Pressure

To evaluate the influence of PAC on PP in patients with hypertension, 3 logistic models were, respectively, constructed

TABLE 2. Multifactor ANOVA Analysis of PP and PAC in Different Postures

Variables	Postures		
	Upright	Seated	Supine
PP ≤ 44 mm Hg (n = 70)	15.76 ± 8.44	10.84 ± 6.12	5.82 ± 2.61
44 mm Hg < PP ≤ 51 mm Hg (n = 63)	17.24 ± 10.92	12.47 ± 7.09	7.36 ± 5.59
PP > 51 mm Hg (n = 62)	23.68 ± 16.81	14.77 ± 8.67	7.49 ± 5.40

PAC = plasma aldosterone concentration, PP = pulse pressure. For the multivariate tests, the value of Hotelling trace was 0.096, *F* value was 3.011 with $P = 0.007$.

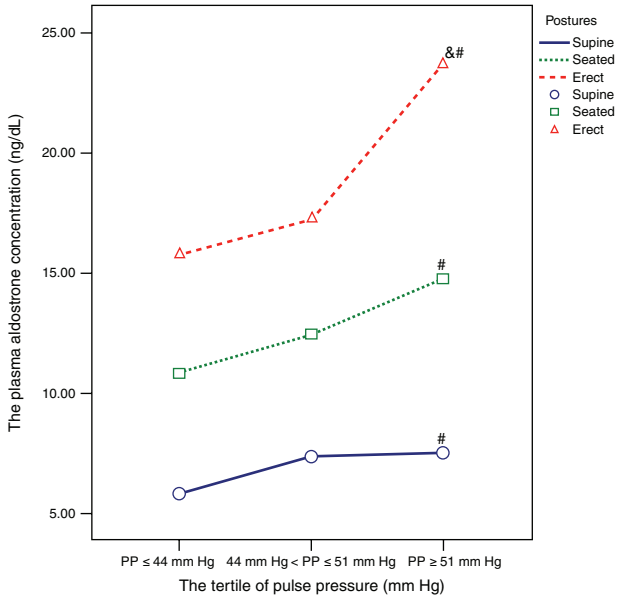

FIGURE 1. Relation between baseline pulse pressure tertile and plasma aldosterone concentrations in upright, seated, and supine postures. #: PP > 51 mm Hg group vs. PP ≤ 44 mm Hg group, *P* value < 0.05; &: PP > 51 mm Hg group vs. 44 mm Hg < PP ≤ 51 mm Hg group, *P* value < 0.05.

with PP ≥ 40 mm Hg or PP < 40 mm Hg as the dependent variable, the continuous variables chosen for the logistic regression were age, serum K^+, body mass index, and PAC in 3 postures independently. The serum K^+ and PAC acted as significant contributing factors to patients with PP ≥ 40 mm Hg despite low odds ratio (Table 4).

DISCUSSIONS

The present study evaluated the relationship between PAC and PP in a special hypertensive population who performed postural stimulation testing. The data indicated that 24-hour PP positively associated with PAC in upright, seated, and supine positions, although the results supported a weak correlation between PAC and PP, the present results may offer a new insight into the effect of PAC on arterial elasticity and stiffness in hypertension population.

TABLE 3. Comparison of PP in Different Levels of PAC in Upright, Seated, and Supine Postures

Postures	Group	24-hr PP (mm Hg)	*P* Value
Upright	PAC ≤ 12 ng/dL	45.81 ± 7.45	
	PAC > 12 ng/dL	49.31 ± 9.34	0.012
Seated	PAC ≤ 12 ng/dL	46.71 ± 7.68	
	PAC > 12 ng/dL	50.67 ± 10.20	0.002
Supine	PAC ≤ 6 ng/dL	46.49 ± 8.78	
	PAC > 6 ng/dL	50.16 ± 8.75	0.004

PAC = plasma aldosterone concentration, PP = pulse pressure. *P* value was the difference between 2 groups with different PAC in upright, seated, and supine postures, respectively.

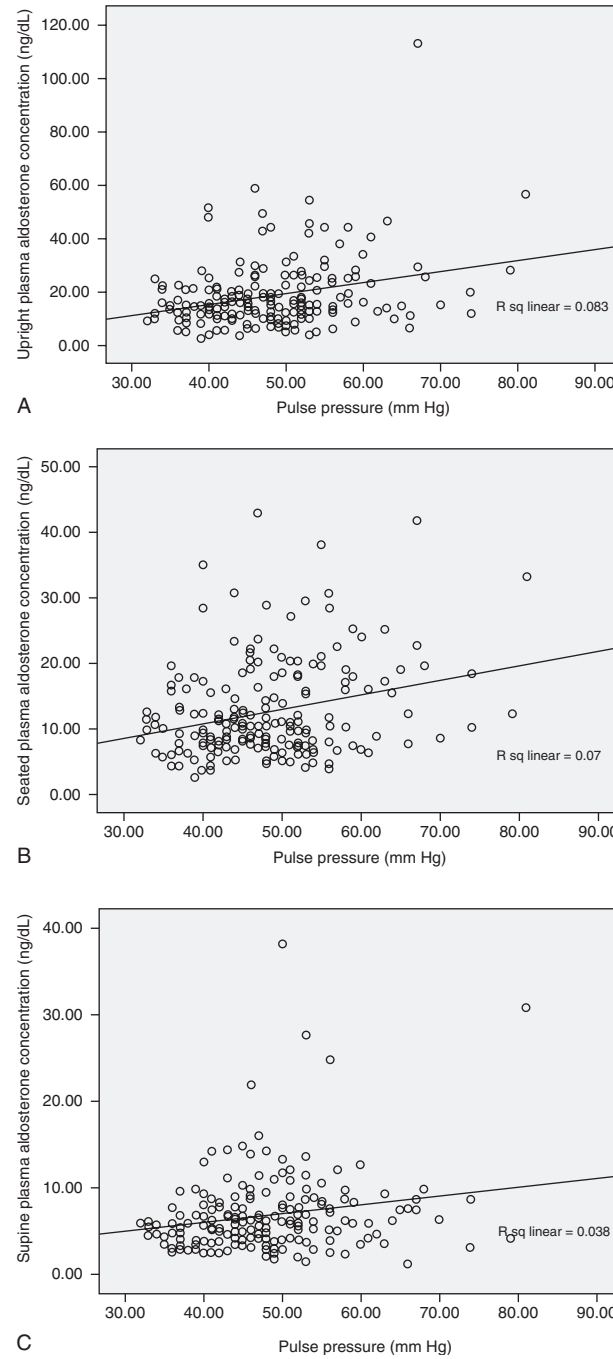

FIGURE 2. Correlation between pulse pressure and plasma aldosterone concentration in upright (panel A), seated (panel B), and supine (panel C) postures.

Aldosterone level is known to be affected by many factors, such as postures, medications, circadian rhythm, potassium, renin level, etc. In the study, the patients were asked to stop the common antihypertensive treatment and correct the hypokalemia to normal level to get an exact measurement of PAC before PST. Furthermore, different to the classical PST, an improved PST was used to measure the PAC in 3 different postures considering the most common postures in one's daily life were

TABLE 4. Logistic Regression Analysis of PP and PAC in Different Postures

Models	Contributing Factors	B	SE	Wald	*P* Value	OR (95% CI)
Model 1	Plasma K^+	−0.961	0.485	3.919	0.048	0.38 (0.15–0.99)
	Upright PAC	0.051	0.018	8.186	0.004	1.05 (1.02–1.09)
	Constant	3.244	1.967	2.720	0.099	25.63
Model 2	Plasma K^+	−0.945	0.482	3.850	0.050	0.39 (0.15–0.99)
	Seated PAC	0.071	0.027	7.206	0.007	1.07 (1.02–1.13)
	Constant	3.221	1.956	2.711	0.100	25.05
Model 3	Plasma K^+	−1.065	0.477	4.992	0.025	0.35 (0.13–0.88)
	Supine PAC	0.092	0.046	4.092	0.043	1.09 (1.00–1.12)
	Constant	3.940	1.913	4.244	0.039	51.41

95% CI = 95% confidence interval, OR = odds ratio, PAC = plasma aldosterone concentration. Model 1: the predictors were age, serum potassium, body mass index, and PAC in upright position. Model 2: the predictors were age, serum potassium, body mass index, and PAC in seated position. Model 3: the predictors were age, serum potassium, body mass index, and PAC in supine position.

nothing more than upright, seated, and supine positions, which minimized the effective factors of PAC and provided more reliable results. Hence, it is believed that the significant association of PAC and PP does exist in patients with hypertension. But, the further mechanism was not discussed in the present study. According to the previous studies, aldosterone may influence PP via several pathways. First, aldosterone causes the oxidation of low-density lipoprotein(LDL) and oxidized LDL can lead to arterial stiffness,[18–20] also, aldosterone induces fibrosis in the heart, blood vessels, and kidney, particularly with high salt intake,[10,21–23] and increases macrophage oxidative stress and atherosclerosis in apolipoprotein $E^{-/-}$ mice.[24] Second, Oberleithner[25] showed that aldosterone remodels human endothelium in vitro, increasing cell size and rigidity, with protein leakage through intercellular gaps that may be the result of increased apical membrane tension. Third, proinflammatory cardiovascular and renal responses to mineralocorticoids, and particularly to aldosterone, have been established.[26–29] In conclusion, there is increasing evidence showing that increased PAC promotes vessel remolding, causes vessel stiffness and elevates PP.

It was reported that the rise of PP begins from middle age and increases progressively.[30] The elevated PP is the consequence of the worse elasticity, as well as the extension ability of the arterial wall in elderly people. However, the age was not detected significant association with PP in the present study, which possibly because the enrolled patients were relatively young (about 43.5-year-old), besides the patients with isolated systolic blood pressure were excluded. We may notice the advancing trend of supine PAC with the increasing PP levels although the *P* value did not reach the statistical significance in ANOVA analysis (Table 1), some reasons could be pointed out. First, most of the patients in the study are individuals whose blood pressure could not be controlled to normal level with cotreatment with 2 kinds of antihypertensive agents (at least), in which a quite proportion of potential endocrine hypertension such as primary aldosteronism may be mixed, so the difference of aldosterone level between groups may disappear. Second, anyway, the aldosterone level was highest in morning and in upright posture considering the influence of circadian rhythm and postures changes. Third, in addition, the body mass index, potassium, etc. were not adjusted in ANOVA analysis in Table 1.

We analyzed the association between PAC and PP on the basis of data of PST and 24-hr ABPM for more reliable information. Although there are still some limitations, on the basis of our study, the patients with hypertension may possibly benefit from the application of aldosterone antagonist to protect the compliance and elasticity of vascular besides antihypertensive treatment.

Study Limitations

Several limitations should be referred to the present study. First, this is an observational study and the number of patients was relatively small, which may account for the weak correlation of PAC with PP. Second, subjects had relative younger ages which may not represent the general hypertension population. Third, PP is reported as one of the risk factors of cardiovascular diseases occurrence and is thought to be a simple and readily obtainable correlate of conduit vessel stiffness. A number of clinical studies have shown that PP is an independent predictor of cardiovascular and all-cause mortality.[31] In the current study, PP is used as one of the markers of artery elasticity and stiffness, although this connection is generally accepted, the relationship is not straightforward and better markers of arterial stiffness are currently used. So, more direct markers of arterial stiffness should be preferably applied in the further studies. Finally, in the present study, mean blood pressure levels rise according to PP levels; thus, aldosterone levels could be potentially related to mean blood pressure more than PP. If blood pressure levels were corrected in the linear multivariate analysis, or groups of patients with different PP levels and similar mean blood pressure were discussed, the information would be more powerful. However, the study mainly concentrated on the association of aldosterone with arterial fibrosis and stiffness which is reflected by PP rather than blood pressure. In addition, the PP was calculated by SBP and DBP, so the relation between blood pressure and PAC was not explored, which would be improved in the further studies.

CONCLUSION

The results indicated that higher PAC was weakly, but significantly, correlated to greater PP regardless of upright, seated, and supine postures, suggesting higher PAC may be a risk factor of reduced arterial elasticity in patients with hypertension.

ACKNOWLEDGMENT

The authors would like to express their sincere gratitude to all the staff at the Center for Diagnosis, Treatment and Research

of Hypertension in Xinjiang for their help with the medical examination and demographic data collection.

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