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Effects of valsartan and indapamide on plasma cytokines in essential hypertension

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Abstract: Objective To investigate and compare the effect of valsartan and indapamide on inflammatory cytokines in hypertension. **Methods** Forty-one untreated patients with mild to moderate hypertension and 20 age- and sex-matched normotensives were enrolled in this study. Hypertensives were treated with indapamide 1.5 mg/d ($n=20$) or valsartan 80 mg/d ($n=21$) for 4 weeks, and blood samples for determining monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1α), sP-selectin, asymmetric dimethylarginin (ADMA), angiotensin Ⅱ (AngⅡ), and 6-keto-PGF1α were collected before the treatment and 4 weeks after the treatment. **Results** Hypertensives exhibited significantly higher blood pressure, as well as elevated plasma levels of MCP-1, MIP-1α, sP-selectin and serum level of ADMA compared with the normotensives. Nevertheless, there was no significant difference in serum 6-keto-PGF1α and AngⅡ between the hypertensives and the normotensives. After the treatment with indapamide or valsartan for 4 weeks, both the systolic and diastolic blood pressures, though still higher than those of the normotensives, decreased markedly. After the treatment with indapamide for 4 weeks, MCP-1, MIP-1α and sP-selectin slightly decreased, but not statistically significant ($P>0.05$). Those cytokines decreased significantly after being treated with valsartan for 4 weeks [(19.16±3.11) pg/mL vs (16.08±2.67) pg/mL, $P<0.05$; (27.74±8.36) pg/mL vs (17.64±7.59) pg/mL, $P<0.05$; (2.67±3.18) pg/mL vs (6.15±2.94) pg/mL, $P<0.01$]. In the 2 treatment groups, 6-keto-PGF1α markedly increased [(61.96±20.81) pg/mL vs (96.72±25.89) pg/mL, $P<0.05$; (63.25±16.92) pg/mL vs (143.22±43.45) pg/mL, $P<0.01$]; ADMA decreased significantly [(1.35±0.74) pg/mL vs (0.98±0.56) μmol/L, $P<0.05$; (1.31±0.68) pg/mL vs (0.71±0.52) μmol/L, $P<0.01$]. Though AngⅡ slightly increased, no statistical significance was found ($P>0.05$). **Conclusion** The levels of MCP-1, MIP-1α, sP-selectin and ADMA were elevated in mild to moderate hypertensives. Valsartan and indapamide have similar blood pressure lowering effect. Valasartan exerts more significant effect on cytokines than indapamide does.

Key words: hypertension; cytokine; valsartan; indapamide; angiotensin Ⅱ

[*J Cent South Univ (Med Sci)*, 2006,31(5):0629-06]

*Received date: 2006-08-27

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Foundation item: This work was supported by a grant from "The Scientific Research Foundation of Sanitary Government of Hunan Province (C2005-011)"

缬沙坦和吲哒啪胺对高血压病患者细胞因子影响的对比研究

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[摘要] 目的:比较吲达帕胺和缬沙坦治疗对高血压病患者外周血中细胞因子单核细胞趋化因子-1(MCP-1)、巨噬细胞炎性蛋白1α(MIP-1α)、可溶性P选择素(sP-selectin)、非对称二甲基精氨酸(ADMA)、血管紧张素Ⅱ(AngⅡ)和6-酮-PGF1α(6-keto-PGF1α)的影响。方法:选取我院门诊健康体检者20例和41例原发性高血压患者,将41例高血压患者随机分为吲哒啪胺组(20例)和缬沙坦组(21例),分别予吲哒啪胺(商品名钠催离)1.5 mg/d和缬沙坦(商品名代文)80 mg/d治疗4周,治疗前和治疗4周后抽血检测MCP-1,MIP-1α,sP-selectin,ADMA,AngⅡ和6-keto-PGF1α含量。结果:同正常血压组相比,高血压病患者外周血中MCP-1,MIP-1α,sP-selectin,ADMA浓度显著增加。吲哒啪胺组治疗前后MCP-1,MIP-1α和sP-selectin浓度无明显变化;而缬沙坦治疗4周后,MCP-1,MIP-1α和sP-selectin浓度与治疗前相比均显著下降[分别为(19.16±3.11) pg/mL vs (16.08±2.67) pg/mL,$P<0.05$;(27.74±8.36) pg/mL vs (17.64±7.59) pg/mL,$P<0.05$;(2.67±3.18) pg/mL vs (6.15±2.94) pg/mL,$P<0.01$]。吲达帕胺和缬沙坦治疗后,ADMA浓度均下降[分别为(1.35±0.74) μmol/L vs (0.98±0.56) μmol/L,$P<0.05$;(1.31±0.68) μmol/L vs (0.71±0.52) μmol/L,$P<0.01$],而6-keto-PGF1α浓度增加,但在缬沙坦组增高更加显著[分别为(61.96±20.81) pg/mL vs (96.72±25.89) pg/mL,$P<0.05$;(63.25±16.92) pg/mL vs (143.22±43.45) pg/mL,$P<0.01$]。两组治疗前后AngⅡ无显著变化。结论:轻中度高血压病患者外周血中细胞因子MCP-1,MIP-1α,sP-selectin和ADMA的浓度增加;缬沙坦和吲哒啪胺具有相似的降压疗效,同时还可降低上述细胞因子水平。

[关键词] 高血压; 细胞因子; 缬沙坦; 吲哚啪胺; 血管紧张素Ⅱ
[中图分类号] R544.1 [文献标识码] A [文章编号] 1672-7347(2006)05-0629-06

There was growing evidence that hypertension, atherosclerosis, was associated with a lowing-degree vascular inflammatory response[1]. In patients with arterial hypertension and/or other major cardiovascular risk factors, plasma levels of chemokines were increased[2-3]. Previous studies included ours had showed that hypertension increases the chemokine, monocyte chemotactic protein-1 (MCP-1) expression in the aorta of rats[4-5], implying inflammatory cytokines and endothelial disfunction may play an important role in the pathogenesis of vascular lesion formation and end-organ damage in hypertension.

Renin-angiotensin system (RAS) plays a key role in many pathophysiological processes, such as atherosclerosis and hypertension. Both experimental and clinical studies revealed that angiotension Ⅱ (AngⅡ), the key effector of the local and circulating RAS, participates in the pathogenesis of hypertension-induced end-organ damage[6]. Several studies showed ACE inhibitors and AT_1 receptor blockers can decrease inflammatory mediators and attenuate vascular inflammation in hypertension[7-8]. Nevertheless, not all AT_1 receptor blockers has the equal efficacy[9].

In this study, we sought to explore the inflammatory markers in hypertensive subjects, and the efficacy and anti-inflammatory profile of the selective AT_1 receptor blocker valsartan.

1 METHODS

1.1 Study population In accordance with the criteria set by the World Health Organization/International Society of Hypertension (WHO/ISH,1999), 41 patients (16 women and 25 men; age 52.9±8.2 years) with mild to moderate hypertension [140≤systolic blood pressure (SBP)≤180 mmHg and 90 mmHg diastolic blood pressure (DBP)≤110 mmHg], as well as 20 age-matched healthy volunteers (8 women and 12 men; age 50.8±4.8 years) were enrolled in this study. All subjects were not received any medical treatment for hypertension, hyperlipidemia, antiplatelet therapy or hormone replacement at least 2 weeks before collecting the blood sample for laboratory measurement.

Baseline characteristics at inclusion were summarized in Table 1.

Patients with clinical signs, symptoms, or laboratory findings suggestive of secondary hypertension were excluded. Other exclusion criteria for all subjects includes smoking, alcohol abuse, chronic infection, diabetes mellitus, chronic obstructive pulmonary disease, hyperthyroidism, renal disease, malignancy, hepatic disease, connective tissue disease, pregnancy, any acute illness. Coronary artery disease or congestive heart failure, evaluated by medical history, exercise stress test, electrocardiogram, echocardiographic examination, and coronary angiography, were also excluded.

The Ethical Committee of Xiangya Hospital, Central South University approved this research protocol. All subjects were given informed consent and studied in our Cardiology Department.

1.2 **Clinical evaluation** Clinical evaluation included blood pressure measurement, physical examination. The blood pressure was measured by cuff sphygmomanometer from right arm in the supine position and under conditions of physical and emotional rest. Systolic and diastolic blood pressures were established by the first and fifth Korotkoff phases respectively on ≥3 successive measurement.

1.3 **Protocol** After withdrawing all drugs for 1 week, hypertensive subjects received indapamide (Servier Pharma Ltd, Beijing) 1.5 mg/d or valsartan (Novartis Pharma Ltd, Beijing) 80 mg/d for 4 weeks and followed up weekly. Blood samples were collected before the treatment and 4 weeks after the treatment.

1.4 **Laboratory measurements** Tea and coffee were withheld for at least 24 h before the study. Blood samples were obtained by standard venipuncture after a 12 h overnight fast from all subjects. The blood samples determining MCP-1 , MIP-1α and sP-selectin were collected and centrifuged at 3 000 r/min for 15 min. Blood samples for Ang Ⅱ measurement were rapidly transferred into prechilled polystyrene tubes containing inhibitor solution (0.3 mol/L disodium EDTA, 50 μL; 0.34 mol/L 8-hydroxyquinoline, 50 μL; 0.32 mol/L Dimercaprol, 25 μL) and centrifuged at 3 600 r/min for 15 min (4 ℃). Blood samples for 6-keto-PGF1α measurement were drawn into tubes containing indomethacin-EDTANa_{12} and centrifuged at 4 500 r/min for 10 min (4 ℃). All samples were frozen at −70 ℃ until assayed.

Plasma MCP-1, MIP-1α and sP-selectin levels were determined by commercially available enzyme-linked immunosorbent assay (ELISA) kits (Genzyme, USA) and performed according to the manufacturer 's protocol.

Serum Ang Ⅱ and 6-keto-PGF1α concentrations were measured by radioimmunoassay with commercial kits (North Biological Research Institute, China). The lower detection limit was 10 pg/mL and 25 pg/mL, respectively. Overall intra-assay and inter-assay variation coefficients were ≤10% and 15% for Ang Ⅱ and ≤3.5% and 10% for 6-keto-PGF1α, respectively. The concentrations were expressed in picograms per milliliter.

The serum samples were deproteined with 5-sulfodalicylic acid and the supernatant was taken for measurement of ADMA concentration with high-performance liquid chromatography (HPLC) according to the method described previously. HPLC was carried out using a Shimadzu LC-6A (Shimadzu corporation Kyoto Japan) liquid chromatograph with Shmadzu SCL-6A system controller and Shimadzu SIC-6A autosampler. Ophthaldiadehyde adducts of methylated amino acids and internal standard ADMA produced by precolumn mixing were monitored using a model RF 530 flouresscence detector set at λ^{ex} = 338 nm and λ^{em} = 425 nm on a resolve C_{18} column. Samples were eluted from the column using a linear gradient containing mobile phase A composed of 0.05 mol/L (pH 6.8) sodium acetate-methanol-tetrahydrofuran and mobile phase B composed of 0.05 mol/L sodium acetate-methanol-tetrahydrofuran at a flow-rate of 1 mL/min.

1.5 **Statistical analysis** The data were presented as $\bar{x} \pm s$ and analyzed with SPSS (version 10). Comparisons between groups were made with One-Way *ANOVA*, followed by q test; comparisons between before-treatment and after-treatment were performed by t test. Statistical significance was considered to be indicated by a two-tailed value of $P < 0.05$.

2 RESULTS

2.1 Baseline characteristics of hypertensive patients and normotensive subjects Patients had significanty higher blood pressure compared with those of normotensives, whereas similar blood pressure were presented between indapamide and valsartan groups. There were no significant difference among 3 groups in age, sex, fast glucose, triglyceride and total cholesterol levels (Table 1).

Table 1 Baseline characteristics of participants ($\bar{x} \pm s$)

Characteristics	normotensive	Indapamide	Valsartan
n	20	20	21
Age (years)	50.8 ± 4.8	52.7 ± 8.0	53.6 ± 6.7
Sex (male/female)	12/8	13/7	12/9
SBP (mmHg)	109.8 ± 13.3	158.5 ± 14.2 *	156.7 ± 11.8 *
DBP (mmHg)	72.2 ± 6.7	92.7 ± 8.6 *	91.6 ± 9.5 *
Fast glucose (mmol/L)	4.33 ± 0.67	4.51 ± 0.69	4.47 ± 0.82
Triglyceride (mmol/L)	1.13 ± 0.30	1.16 ± 0.46	1.08 ± 0.59
total cholesterol (mmol/L)	4.04 ± 0.42	4.12 ± 0.53	4.09 ± 0.51

Compared with normotensive group, * $P < 0.05$

2.2 Levels of cytokines in hypertensives and normotensives Plasma MCP-1, MIP-1α, sP-selectin and serum ADMA levels were significantly increased in all hypertensives compared with that in normotensives ($P < 0.01$). Nevertheless, there was no significant difference between indapamide and valsartan groups. No statistical significant difference in serum Ang Ⅱ and 6-keto-PGF1α concentrations were found among the 3 groups ($P > 0.05$, Table 2).

2.3 Effects of indapamide and valsartan on blood pressure After treated with indapamide 1.5 mg/d or valsartan 80 mg/d for 4 weeks, SBP and DBP, though still higher than normotensives, both decreased significantly ($P < 0.05$). Nevertheless no statitical significance were found in indapamide and valsartan groups ($P > 0.05$, Table 3).

2.4 Effects of indapamide and valsartan on the levels of cytokines After treated with indapamide 1.5 mg/d for 4 weeks, MCP-1, MIP-1α and sP-selectin slightly decreased, whereas has no statistical significance ($P > 0.05$). Nevertheless, these chemokines decreased significantly after treated with valsartan for 4 weeks [(19.16 ± 3.11) pg/mL vs (16.08 ± 2.67) pg/mL, $P < 0.05$; (27.74 ± 8.36) pg/mL vs (17.64 ± 7.59) pg/mL, $P < 0.05$; (12.67 ± 3.18) pg/mL vs (6.15 ± 2.94) pg/mL, $P < 0.01$; respectively)].

ADMA decreased significantly [(1.35 ± 0.74) μmol/L vs (0.98 ± 0.56) μmol/L, $P < 0.05$; (1.31 ± 0.68) μmol/L vs (0.71 ± 0.52) μmol/L, $P < 0.01$, respectively)]; and 6-keto-PGF1α marked increased [(61.96 ± 20.81) pg/mL vs (96.72 ± 25.89) pg/mL, $P < 0.05$; (63.25 ± 16.92) pg/mL vs (143.22 ± 43.45) pg/mL, $P < 0.01$, respectively)] after treated with indapamide or valsartan for 4 weeks. Though Ang Ⅱ slightly increased, no statistical significance was found ($P > 0.05$).

The level of 6-keto-PGF1α in group treated with valsartan was higher than that in group treated with indapamide ($P < 0.05$).

Table 2 Baseline and follow-up levels of cytokines of participants ($\bar{x} \pm s$)

Parameters	Normotensives ($n = 20$)	Indapamide ($n = 20$)		Valsartan ($n = 21$)	
		before-treatment	After-treatment	before-treatment	After-treatment
MCP-1 (pg/mL)	15.45 ± 1.13	18.37 ± 2.38 * *	17.1 ± 2.39 △	19.16 ± 3.11 * *	16.08 ± 2.67 #
MIP-1α (pg/mL)	15.11 ± 3.72	28.47 ± 7.07 * *	27.64 ± 6.51 △	27.74 ± 8.36 * *	17.64 ± 7.59 #
6-keto-PGF1α (pg/mL)	64.82 ± 17.19	61.96 ± 20.81	96.72 ± 25.89 #	63.25 ± 16.92	143.22 ± 43.45 ##▲
sP-selectin (pg/mL)	3.67 ± 1.52	11.09 ± 3.58 * *	10.74 ± 3.26 △	12.67 ± 3.18 * *	6.15 ± 2.94 ##
ADMA (μmol/L)	0.57 ± 0.36	1.35 ± 0.74 * *	0.98 ± 0.56 #	1.31 ± 0.68 * *	0.71 ± 0.52 ##
Ang Ⅱ (pg/mL)	32.98 ± 14.61	33.17 ± 11.59	36.85 ± 12.64	34.78 ± 13.52	37.56 ± 14.83 * *

Compared with normotensives, * * $P < 0.01$; Compared with before-treatment, △ $P > 0.05$, # $P < 0.05$, ## $P < 0.01$; Compared with indapamide treatment, ▲ $P < 0.05$

Table 3 Effect of indapamide and valsartan on blood pressure in hypertensives ($\bar{x} \pm s$, mmHg)

Groups	n	SBP		DBP	
		before-treatment	After-treatment	before-treatment	After-treatment
Normotensives	20	109.8 ± 13.3		72.2 ± 6.7	
Indapamide	20	158.5 ± 14.2 *	137.5 ± 12.4 *#	92.7 ± 8.68 *	85.6 ± 7.9 *#
Valsartan	21	156.7 ± 11.8	138.4 ± 10.7 *#	91.6 ± 9.5	86.7 ± 9.3 *#

Compared with normotensives, * $P < 0.05$; Compared with before-treatment, # $P < 0.05$

3 DISCUSSION

Increasing evidence demonstrated that impaired endothelial function and exaggerated inflammatory cytokines occurred in circulation and vessel wall, followed with migration of monocytes into the vessel wall mediated in part by MCP-1, were presented in hypertension[3-4,10-12]. Previous study found that untreated patients with mild to moderate hypertension without coronary artery disease have elevated plasma levels of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), MIP-1α, RANTES, soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1). The plasma levels of these chemokines are related to serum ET-1 activity, which suggests an interaction between neurohormonal ' activation and inflammation in hypertension[3]. MCP-1 and monocyte/macrophage infiltration augmented in aortic wall of several hypertensive models[4-5]. In agreement with previous observations, the present study indicated that the plasma concentration of MCP-1, MIP-1α, sP-selectin and the serum level of ADMA were significant elevated in mild to moderate hypertensives as compared with normotensives. Nevertheless, the expression of 6-keto-PGF1α and Ang Ⅱ showed no statistical significance. Although hypertension is an well established risk factor for the development of atherosclerosis, the underlying molecular mechanisms have not been clearly elucidated. The well known association between non-infected inflammation and atherosclerotic lesion formation may provide potential mechanistic insights for hypertension as a risk factor for the development of atherosclerosis. However, the precise mechanism and clinical significance of elevated inflammatory cytokines in hypertension still deserve further investigation.

Hypertension, particularly in the presence of an activated renin-angiotensin system, was an important risk factor for the end-organ damage[13]. Ang Ⅱ may contribute to the development of vascular and myocardial structural changes in hypertension. Several angiotensin-converting enzyme inhibitors (ACEIs) and Ang Ⅱ receptor 1 antagonist (ARB) decreased circulatory concentration of cytokines, such an MCP-1, IL-6, CRP and PAI-1 levels in essential hypertensive patients[8-9,12,14]. However, ARBs shown different profile on cytokines in different researches[12,14-15]. In our present study, we demonstrated that valsartan, an high selective ARB, significantly decreased the circulatory levels of MCP-1, MIP-1α, sP-selectin and ADMA as well as increased 6-keto-PGF1α concentration in hypertension. On the other hand, indapamide though decreased blood pressure to the same level, the levels of MCP-1, MIP-1α, sP-selectin only slightly decreased. The beneficial effects of valsartan on cytokines and endothelial function may have implications for vascular remodeling and atherosclerotic lesion formation and for providing end-organ protection in hypertension. However, this may not be fully explained now by their antihypertensive effects alone. Recently, Li et al[16] suggested that valsartan has direct anti-inflammatory effects in hypertension which are unrelated to its blood pressure-lowering effects.

Abundant observations reported that impaired endothelial function was observed in hypertension and atherosclerosis. Growing investigations have shown that ADMA, an endogenous NOS inhibitor was elevated in hypertension[17-18]. ACEIs administration significantly decreased serum ADMA level in hypertension[18]. Previous study has shown that 13, 14-dihydro-15-keto-PGF2α, 6-keto-PGF1α and 8-isoprostane levels were lower in aorta from hypertensive rats than those from normotensive rats[19]. PGI2 reduction seemed to be one of the main factor accounting for endothelial dysfunction in hypertensive rats, whereas other prostanoids besides PGI2 appeared to be involved in endothelial dysfunction under normotensive conditions[20]. ACEIs effectively inhibited ACE activity both in plasma and in tissues, meanwhile, increased 6-keto-PGF1α levels in male rats[21]. Then, ADMA and 6-keto-PGF1α may involve in the development of endothelial dysfunction in hypertension and ACEIs reserved endothelial function in hypertension may be related to reduction of ADMA and augmentation of 6-keto-PGF1α. In the present study, we found that though 6-keto-PGF1α, a stable metabolite of PGI2, showed no statistical significance between normotensive and hypertensive subjects, increased markedly and ADMA significantly decreased after treated with indapamide and valsartan for 4 weeks. Decreased ADMA may facilitate nitric oxide (NO) gener-

ation, implying that lowing blood pressure could reserve endothelial function. Higher level of 6-keto-PGF1α was shown in group treated with valsartan than that with indapamide, implying that valsartan may reserve endothelial function besides lowering blood pressure.

In summary, we have detected significant higher levels of MCP-1 MIP-1α, sP-selectin and ADMA in mild to moderate hypertension as compared with normotensive subjects, which hint that endothelial dysfunction occurred in hypertension and those cytokines may play an important role in the development of hypertensive vascular lesion. Valsartan significantly decreased those cytokines besides effectively lowering blood pressure.

References:

[1] Alexander R W. Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: a new perspective[J]. Hypertension, 1995, 25(2): 155-161.

[2] Parissis J T, Venetsanou K F, Kalantzi M V, et al. Serum profiles of granulocyte-macrophage colony-stimulating factor and C-C chemokines in hypertensive patients with or without significant hyperlipidemia[J]. Am J Cardiol, 2000, 85(6): 777-779.

[3] Parissis J T, Korovesis S, Giazitzoglou E, et al. Plasma profiles of peripheral monocyte-related inflammatory markers in patients with arterial hypertension. Correlations with plasma endothelin-1[J]. Int J Cardiol, 2002, 83(1): 13-21.

[4] Xie Q Y, Ming S, Yang T L, et al. Losartan reduces monocyte chemoattractant protein-1 expression in aortic tissues of 2K1C hypertensive rats[J]. Int J Cardiol, 2006, 110(1): 60-66.

[5] Capers Q 4th, Alexander R W, Lou P, et al. Monocyte chemoattractant protein-1 expression in aortic tissues of hypertensive rats[J]. Hypertension, 1997, 30(6): 1397-1402.

[6] Lindpaintner K, Ganten D. The cardiac renin-angiotensin system. An appraisal of present experimental and clinical evidence[J]. Circ Res, 1991, 68(4): 905-921.

[7] da Cunha V, Tham D M, Martin-McNulty B, et al. Enalapril attenuates angiotensin II-induced atherosclerosis and vascular inflammation[J]. Atherosclerosis, 2005, 178(1): 9-17.

[8] Fliser D, Buchholz K, Haller H. Antiinflammatory effects of angiotensin II subtype 1 receptor blockade in hypertensive patients with microinflammation[J]. Circulation, 2004, 110(9): 1103-1107.

[9] Jilma B, Li-Saw-Hee F L, Wagner O F, et al. Effects of enalapril and losartan on circulating adhesion molecules and monocyte chemotactic protein-1[J]. Clin Sci, 2002, 103(2): 131-136.

[10] Nomura S, Shouzu A, Omoto S, et al. Long-term treatment with nifedipine modulates procoagulant marker and C-C chemokine in hypertensive patients with type 2 diabetes mellitus[J]. Thromb Res, 2005, 115(4): 277-285.

[11] Goonasekera C D, Shah V, Rees D D, et al. Vascular endothelial cell activation associated with increased plasma asymmetric dimethyl arginine in children and young adults with hypertension: a basis for atheroma?[J]. Blood Press, 2000, 9(1): 16-21.

[12] Vazquez-Oliva G, Fernandez-Real J M, Zamora A, et al. Lowering of blood pressure leads to decreased circulating interleukin-6 in hypertensive subjects[J]. J Hum Hypertens, 2005, 19(6): 457-462.

[13] Alderman M H, Madhavan S, Ooi W L, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension[J]. N Engl J Med, 1991, 324(16): 1098-1104.

[14] Koh K K, Han S H, Chung W J, et al. Comparison of effects of losartan, irbesartan, and candesartan on flow-mediated brachial artery dilation and on inflammatory and thrombolytic markers in patients with systemic hypertension[J]. Am J Cardiol, 2004, 93(11): 1432-1435, A1410.

[15] Schupp M, Janke J, Clasen R, et al. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity[J]. Circulation, 2004, 109(17): 2054-2057.

[16] Li Q Z, Deng Q, Li J Q, et al. Valsartan reduces interleukin-1beta secretion by peripheral blood mononuclear cells in patients with essential hypertension[J]. Clin Chim Acta, 2005, 355(1-2): 131-136.

[17] Curgunlu A, Uzun H, Bavunoglu I, et al. Increased circulating concentrations of asymmetric dimethylarginine (ADMA) in white coat hypertension[J]. J Hum Hypertens, 2005, 19(8): 629-633.

[18] Napoli C, Sica V, de Nigris F, et al. Sulfhydryl angiotensin-converting enzyme inhibition induces sustained reduction of systemic oxidative stress and improves the nitric oxide pathway in patients with essential hypertension[J]. Am Heart J, 2004, 148(1): 172-179.

[19] Alvarez Y, Briones A M, Balfagon G, et al. Hypertension increases the participation of vasoconstrictor prostanoids from cyclooxygenase-2 in phenylephrine responses[J]. J Hypertens, 2005, 23(4): 767-777.

[20] Blanco-Rivero J, Cachofeiro V, Lahera V, et al. Participation of prostacyclin in endothelial dysfunction induced by aldosterone in normotensive and hypertensive rats[J]. Hypertension, 2005, 46(1): 107-112.

[21] Torsello A, Locatelli V, Cella S G, et al. Moexipril and quinapril inhibition of tissue angiotensin-converting enzyme activity in the rat: evidence for direct effects in heart, lung and kidney and stimulation of prostacyclin generation[J]. J Endocrinol Invest, 2003, 26(1): 79-83.

(Edited by GUO Zheng)