ORIGINAL ARTICLE

Effect of Nisoldipine and Olmesartan on Endothelium-Dependent Vasodilation in Essential Hypertensive Patients

Duo Wei,¹ Wan-Yuan He² & Qian-Zhou Lv¹¹Department of Pharmacy, Zhongshan, Hospital, Fudan University, Shanghai, China²Department of Ultrasound, Zhongshan, Hospital, Fudan University, Shanghai, China**Keywords**

Asymmetric dimethylarginine; Endothelin; Nisoldipine; Olmesartan; Vasodilation.

Correspondence

Qian-Zhou Lv, Professor, Department of Pharmacy, Zhongshan Hospital, Fudan University, 180 Feng Lin Road, Shanghai 200032, China.

Tel: +86-21-34160880;

Fax: +86-21-34160880;

E-mail: lv.qianzhou@zs-hospital.sh.cn

Received 10 November 2011; revision 7

December 2011; accepted 8 December 2011

doi: 10.1111/j.1755-5949.2012.00304.x

SUMMARY

Aims: To investigate whether nisoldipine and olmesartan improve endothelial function, decrease asymmetric dimethylarginine (ADMA) and alleviate the inflammatory and oxidative process. **Methods:** Fifty-five essential hypertensive patients were randomized to receive nisoldipine or olmesartan for 8 weeks according to a parallel-group, active-controlled, single blind study, and 28 matched normotensive subjects served as healthy controls. Flow-mediated dilation (FMD), and plasma levels of nitric oxide (NO), endothelin-1 (ET-1), high-sensitive C-reactive protein (hs-CRP), 8-isoprostane (also named 8-isoPGF2 α), and ADMA were determined. **Results:** At baseline, the plasma levels of ADMA, ET-1, hs-CRP, and 8-isoPGF2 α were markedly higher in patients with essential hypertension than in normotensive subjects ($P < 0.05$). A significant positive correlation was observed between plasma levels of ET-1 and ADMA in patients with essential hypertension, but not in normotensive subjects. The NO plasma concentrations were significantly lower in patients with essential hypertension than in normotensive subjects. Furthermore, hypertensive subjects demonstrated significantly lower FMD than healthy control ($P < 0.05$). Nisoldipine and olmesartan significantly and similarly reduced blood pressure in patients with essential hypertension ($P < 0.001$). At the end of the 8-week treatment, plasma ADMA and ET-1 levels were decreased significantly ($P < 0.01$). FMD increased significantly in nisoldipine or olmesartan-treated patients ($P < 0.05$). A significant decrease in plasma hs-CRP contents was observed in patients receiving nisoldipine ($P < 0.05$). **Conclusion:** The findings demonstrate that nisoldipine and olmesartan both improve FMD in patients with essential hypertension. This may be associated with decreased circulating levels of CRP, ET-1, and ADMA.

Introduction

Essential hypertension is characterized by an impairment of endothelial function [1], which plays a pivotal role in the initiation and development of atherosclerotic lesions and is predictive of clinical events and stroke [2,3]. This is especially relevant because hypertension is a major factor for stroke [4]. Under physiological conditions, the endothelium can produce relaxing and contracting factors in the regulation of vascular tone. Nitric oxide (NO) is the major endothelium-derived relaxing factor and patients with essential hypertension have impaired endothelium-dependent vasodilation, largely because of decreased activity of NO [5,6]. The major endothelium-derived contracting factor is endothelin-1 (ET-1) and increased ET-1 release is also a contributory factor to endothelial dysfunction [7,8]. However, the precise mechanisms underlying impaired endothelial function in hypertensive vessels have not been fully characterized. Enhanced vascular oxidative stress, which generates superoxide anion that in-

activates endothelium-derived NO, may impair endothelial function [9]. The NO synthase inhibitor, asymmetric dimethylarginine (ADMA), inhibits endothelial NO synthase (eNOS), reducing NO bioavailability and consequently leading to endothelial dysfunction [10]. The inflammatory response may down-regulate eNOS by decreasing eNOS activity and NO bioactivity, and thus become involved in endothelial dysfunction [11].

Nisoldipine is a dihydropyridine-based calcium channel blocker. Nisoldipine ameliorates endothelial function through either mobilizing endothelial progenitor cells to the circulation [12] or increasing NO bioavailability [13]. Nisoldipine was found to suppress the production of ET from cultured human endothelial cells [14] and improve NO bioavailability *in vitro* [15]. However, whether nisoldipine improves endothelial function in essential hypertensive patients remains unknown. Olmesartan is an angiotensin-II receptor blocker. Olmesartan has been shown to improve endothelial function in patients with essential hypertension [16] and this improvement is independent of its blood pressure (BP)-lowering effects,

probably by militating against oxidative stress [17]. Thus, it is conceivable that reversing endothelial dysfunction could represent an adjunctive target for antihypertensive treatment.

Here, we carried out a randomized, parallel-group, active-controlled, single blind study in fifty-five patients with grade I or II essential hypertension who were treatment naïve or had never received previous therapy with nisoldipine or olmesartan. We aimed to investigate whether nisoldipine and olmesartan improve endothelial function, decrease ADMA, and alleviate the inflammatory and oxidative process. Toward this end, we measured the plasma levels of NO, ET-1, and ADMA, and the plasma levels of high-sensitive C-reactive protein (hs-CRP) and the oxidative stress marker, 8-isoprostane (8-isoPGF 2α), in essential hypertensive patients and further evaluated flow-mediated dilation (FMD) in the brachial artery (BA).

Subjects and Methods

Patients

This randomized, parallel-group, and active-controlled study was carried out at the Shanghai Changfeng Study [18] and Cardiovascular Division of Zhongshan Hospital, Fudan University, Shanghai, China. Grade I or II essential hypertension was diagnosed according to the WHO/ISH criteria [19]. Patients eligible for inclusion were outpatients with grade I or II essential hypertension (mean sitting systolic BP [msSBP] ≥ 140 mmHg and < 180 mmHg and/or diastolic BP [msDBP] ≥ 90 mmHg and < 110 mmHg) at outpatient visit without clinically evident organ damage. Patients were included if they were treatment naïve or if they reported a history of discontinued or ineffective pharmacological antihypertensive treatment but had never received previously a calcium antagonist or an angiotensin-II receptor antagonist. The exclusion criterion were the presence of hypercholesterolemia (total cholesterol [TC] > 6.5 mmol/L [250 mg/dL]), a history of smoking (more than five cigarettes per day) or alcohol consumption (> 80 g/day), and the presence of diabetes mellitus, secondary hypertension, coronary disease or other cardiac diseases, stroke, glaucoma, or hepatic and renal diseases. Postmenopausal women who were on hormone replacement therapy were also excluded. Fifty-five patients with essential hypertension met the eligibility requirements and were included in this study. Twenty-eight matched healthy persons were included as the normal control subjects. Subjects were defined as normal if BP values were $< 130/85$ mmHg. BP was determined from the mean of three measurements made at 1-min intervals after the subjects had been seated for 10 min. The protocol was approved by the Ethical Committee of Zhongshan Hospital, Fudan University and was conducted in accordance with Good Clinical Practice and in compliance with the Declaration of Helsinki and all subjects gave their written informed consent before undergoing any study procedure.

Study Design

Hypertensive patients were treated with nisoldipine (10 mg) or olmesartan (20 mg) once daily ($n = 27$ for the nisoldipine group; $n = 28$ for the olmesartan group) according to a randomized,

single-blinded design. Patients were visited every 2 weeks and nisoldipine or olmesartan was titrated to 20 or 40 mg/day, with the addition of hydrochlorothiazide (12.5–25 mg/day) if necessary, to maintain BP below 140/90 mmHg. The whole duration of treatment was 8 weeks. Each subject underwent detailed characterization at baseline including full lipid profile (TC, triglyceride [TG], low density lipoprotein [LDL] cholesterol, and high density lipoprotein [HDL] cholesterol), and fasting plasma glucose (FPG). The plasma concentrations of NO, hs-CRP, ET-1, ADMA, and 8-isoprostane (8-isoPGF 2α) were measured at baseline and at the end of 8-week therapy. In addition, endothelium-dependent and independent vascular response was evaluated at baseline and at the end of 8-week therapy as detailed later.

Evaluation of FMD

Endothelial function was evaluated by the measurement of FMD as previously described [20]. A B-mode scan of the right BA was obtained in the longitudinal section 2–5 cm above the elbow by the same operator using a 7.5-MHz linear array transducer held at the same point throughout the scan. Simultaneous electrocardiographic recordings were obtained and displayed on the ultrasound system (Philips-iu22, Eindhoven, the Netherlands) video monitor. Imaging studies were performed using the lower arm occlusion technique. After 1 min of acquisition (the basal diameter), a BP cuff was inflated to 280 mmHg for 5 min; and, following deflation, the BA was imaged continuously for 2 min. FMD was expressed as the percentage of change in the BA diameter from the baseline to 45 to 60 seconds (the maximal vessel diameter) after deflation of the cuff. A repeat baseline scan was obtained after a 15-min rest. Endothelium-independent dilation was obtained by the administration of sublingual glyceryl trinitrate (0.5 mg). A further scan was performed 4 min later to assess the maximal BA dilator response to glyceryl trinitrate. Scans were recorded and analyzed offline. The variability was 12% with a mean difference of 0.8% between the two measurements.

Laboratory Parameters

Fasting blood samples were drawn under standardized conditions and stored at -80°C until further analysis. Assays for lipid profile and FPG were performed by the Department of Laboratory Medicine of Zhongshan Hospital. Plasma ADMA was measured by competitive ELISA [21] (Cusabio, Wuhan, China) with a standard range from 7.8 to 500 ng/mL and a detection limit of 2 ng/mL. Hs-CRP was measured using a particle enhanced immunoturbidimetric assay (DiaSys Diagnostic Systems, Shanghai, China) on the HI-7600–120 Analyser (HITA). The plasma concentrations of 8-isoPGF 2α were determined using a commercial competitive enzyme immunoassay kit (Cayman Chemicals, MI, USA). Before the assay procedures, samples were subjected to purification by means of SPE Cartridges (C-18) (Cayman Chemicals). Levels of ET-1 were estimated using a commercial ELISA kit (Cusabio). NO was measured by the colorimetric method (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Absorbance was read at 550 nm in Flexstation 3.0 (Molecular Devices, CA, USA).

Statistical Analysis

Data analysis was performed with the SPSS 16.0 software for Windows. Data were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range) for variables that deviated from normal distribution. Student's *t*-tests or the Wilcoxon rank sum tests (2-tailed) were used to analyze differences in continuous variables between hypertensive patients and normotensive subjects. Categorical variables were compared between groups by the χ^2 -test. Changes in parameters between the baseline and the end of the 8-week nisoldipine or olmesartan treatment were analyzed using the paired Student's *t*-test or the Wilcoxon rank sum test where appropriate. Baseline data for the nisoldipine group, the olmesartan group, and the normotensive group were analyzed by 1-factor analysis of variance or nonparametric Kruskal–Wallis test where appropriate. Pearson or Spearman correlation analysis was applied to assess the relationships among variables. Statistical significance was accepted at $P < 0.05$.

Results

Demographic and Clinical Characteristics of Study Participants

Fifty-five patients with essential hypertension and 28 normotensive subjects were included in this study and the demographic and clinical characteristics of these study participants are shown in Table 1. The SBP and DBP of patients with essential hypertension (SBP, 148 ± 9.1 mmHg and DBP, 87.8 ± 9.0 mmHg) were significantly higher than those of the normotensive subjects (SBP, 110 ± 10.5 mmHg and DBP, 70.7 ± 8.9 mmHg) ($P < 0.001$). The age, sex, BMI, TC, TG, HDL-cholesterol, LDL-cholesterol, FPG, and heart rate were similar and within a normal range between normotensive subjects and patients with essential hypertension at baseline (Table 1) and at the end of treatment (data not shown).

Table 1 Demographic and clinical characteristics of the study participants

	Essential hypertensive subjects (n = 55)	Normotensive subjects (n = 28)	P value
Sex (male/female)	41/14	18/10	0.330
Age (years)	58.6 ± 7.27	56.3 ± 4.71	0.089
BMI (kg/m ²)	24.8 ± 2.76	24.5 ± 3.01	0.647
Total cholesterol (mmol/L)	4.89 ± 0.84	4.60 ± 0.71	0.124
Triglycerides (mmol/L)	1.71 ± 0.85	1.38 ± 0.10	0.122
HDL cholesterol (mmol/L)	1.24 ± 0.34	1.38 ± 0.38	0.080
LDL cholesterol (mmol/L)	2.87 ± 0.68	2.66 ± 0.61	0.160
Plasma glucose (mmol/L)	5.18 ± 0.56	5.44 ± 0.58	0.053
SBP (mmHg)	148 ± 9.1	110 ± 10.5	<0.001
DBP (mmHg)	87.8 ± 9.0	70.7 ± 8.9	<0.001
Heart rate (beats/minute)	73.2 ± 8.0	73.0 ± 6.7	0.878

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Data are given as mean $\pm$ SD.

P value for difference between essential hypertensive patients and normotensive subjects.

Figure 1 Correlation between ADMA (asymmetric dimethylarginine) and ET-1 (endothelin-1) levels in hypertensive patients at baseline.

Basal Laboratory Parameters and Endothelial Function Between Normotensive Subjects and Essential Hypertensive Patients

At baseline, the plasma levels of ADMA were markedly higher in patients with essential hypertension (41.0 ± 13.3 ng/mL) than in normotensive subjects (25.3 ± 9.09 ng/mL) ($P < 0.001$). The plasma levels of ET-1 were significantly higher in patients with essential hypertension (2.25 [range, 1.96 – 3.23] pg/mL) than in normotensive subjects (1.22 [range, 1.08 – 1.37] pg/mL; $P < 0.001$). In addition, a significant positive correlation was observed between plasma ET-1 and ADMA levels in patients with essential hypertension, which was not observed in normotensive subjects (Figure 1). The plasma concentrations of 8-isoPGF 2α were noticeably higher in patients with essential hypertension (35.8 [range, 28.6 – 45.3] pg/mL) than in normotensive subjects (26.8 [range, 15.7 – 36.5] pg/mL; $P < 0.01$). The plasma concentrations of hs-CRP were noticeably higher in patients with essential hypertension (1.00 [range, 0.50 – 2.30] mg/dL) than in normotensive subjects (0.60 [range, 0.25 – 1.58] mg/dL; $P < 0.05$). On the other hand, the plasma concentrations of NO were significantly lower in patients with essential hypertension (42.6 [range, 24.0 – 79.9] μ mol/L) than in normotensive subjects (67.6 [range, 60.4 – 155] μ mol/L; $P < 0.01$). Furthermore, normotensive subjects demonstrated significantly higher FMD ($13.4 \pm 5.50\%$) and Nitroglycerin-mediated dilation (NMD) ($18.6 \pm 9.11\%$) than patients with essential hypertension ($10.4 \pm 3.91\%$) and ($13.1 \pm 6.36\%$) ($P < 0.05$), although no difference was noted in the diameter of the BA between patients with hypertension (4.22 ± 0.57 mm) and normotensive subjects (4.02 ± 0.49 mm) ($P > 0.05$).

Nisoldipine and Olmesartan Similarly Reduce BP in Patients with Essential Hypertension

Thirty-six patients with essential hypertension had never been treated and 19 patients reported a history of discontinued or ineffective pharmacological antihypertensive treatment. These 55 patients were randomized to receive nisoldipine ($n = 27$) or olmesartan ($n = 28$) and 48 patients completed the treatment. Altogether, 20 patients received nisoldipine 10 mg/day,

Figure 2 (A) Values of SBP (systolic blood pressure) for hypertensive patients at baseline and 8-week treatment by nisoldipine or olmesartan. Data are given as mean $\pm$ SD. *P* value for difference between baseline and 8-week later. (B) Values of DBP (diastolic blood pressure) for hypertensive patients at baseline and 8-week treatment by nisoldipine or olmesartan. Data are given as mean $\pm$ SD. *P* value for difference between baseline and 8-week later.

21 patients received olmesartan 20 mg/day, 3 patients received nisoldipine 20 mg/day plus hydrochlorothiazide 25 mg/day, and 4 patients received olmesartan 40 mg/day plus hydrochlorothiazide 25 mg/day. Compared with SBP and DBP at baseline, both nisoldipine and olmesartan significantly reduced DBP and SBP in the patients: with nisoldipine, SBP from 148 ± 9.63 to 121 ± 11.2 mmHg, DBP from 87.7 ± 10.0 to 77.4 ± 6.55 mmHg; with olmesartan, SBP from 149 ± 7.79 to 119 ± 9.87 mmHg, DBP from 88.7 ± 8.04 to 73.4 ± 6.41 mmHg (all $P < 0.001$) (Figure 2A,B), although no significant difference in the levels of heart rate was observed between the two treatment groups ($P > 0.05$).

Nisoldipine and Olmesartan Suppress Plasma ADMA and ET-1 Levels and Improve FMD in Patients with Essential Hypertension

At baseline, there were no significant differences in SBP, DBP, FMD, circulating levels of NO, ET-1, 8-iso-PGF 2α , and ADMA between the two treatment groups (Table 2, Figures 2A,B and 3). Plasma hs-CRP levels were markedly lower in the olmesartan group compared to the nisoldipine group ($P < 0.05$) (Table 2). At the end of the 8-week therapy, although plasma NO tended to increase and plasma 8-iso-PGF 2α levels tended to decrease after nisoldipine or olmesartan treatment, changes in the plasma con-

centrations of NO and 8-iso-PGF 2α were not statistically significant before treatment and at the end of treatment ($P > 0.05$). There was a significant decrease in plasma hs-CRP contents only in patients receiving nisoldipine ($P < 0.05$). At the end of the 8-week treatment, plasma ET-1 and ADMA levels decreased significantly in patients receiving nisoldipine or olmesartan ($P < 0.01$) (Table 2). Furthermore, compared with that at baseline, the diameter of the BA was not significantly changed at the end of 8-week treatment with either nisoldipine or olmesartan ($P > 0.05$) (data not shown). FMD, on the other hand, increased significantly in nisoldipine-treated patients from $10.6 \pm 3.51\%$ before the start of treatment to $14.6 \pm 8.13\%$ at the end of treatment ($P < 0.05$) or in olmesartan-treated patients from $9.79 \pm 3.92\%$ at baseline to $12.7 \pm 4.89\%$ at the end of treatment ($P < 0.05$) (Figure 3) whereas no difference was noted in the BA dilator response to glyceryl trinitrate before and after treatment ($P > 0.05$) (data not shown).

Discussion

Essential hypertension is characterized by an impairment of endothelial function. In agreement with previous observations [22,23], we demonstrated here elevated plasma levels of ET-1 and reduced NO levels and FMD in patients with essential hypertension, suggesting the presence of endothelial dysfunction in the patients. In addition, we present the first direct evidence that the calcium channel blocker nisoldipine markedly suppresses plasma ADMA levels, which could contribute to nisoldipine-induced improvement in endothelial function in hypertensive patients. We further identified a significant correlation between plasma ADMA and ET-1 levels in hypertensive patients. Such a positive correlation has previously been demonstrated in congestive heart failure patients [24]. Our findings support a contributory role of ET-1 in endothelial dysfunction in hypertension. We further found that 8-week therapy with nisoldipine or olmesartan could significantly decrease plasma ET-1 concentrations, which may contribute to improve endothelium-dependent vasodilation as evidenced by increased FMD. A previous report showed that a 6-week treatment with nisoldipine did not modify FMD in the BA [25]. This is different from the current observation, which may be caused by the shorter treatment period in that study. Indeed, a 6-week treatment with nisoldipine also failed to significantly lower BP [25].

Our results that olmesartan can improve FMD and decrease plasma ET-1 levels in essential hypertensive patients are consistent with previous observations [26,27]. Angiotensin II can promote endothelial dysfunction, both by increasing oxygen free radicals and ET productions [28]. The underlying mechanisms may involve olmesartan-induced reduction in AT1 receptor activation, which may interfere with the interaction between angiotensin II and endothelial function and inhibit angiotensin II-induced increases in ET-1 levels. Although there was significant lower GTN in hypertensive patients than normotensive subjects at baseline, we found that nisoldipine and olmesartan exert no effect on the vasodilatory response to glyceryl trinitrate, which acts directly on smooth muscle cells as an NO donor, excluding altered smooth muscle cell responsiveness as a possible cause of nisoldipine or olmesartan-induced improvement in endothelial function. Enhanced vascular oxidative stress, which generates superoxide anion that inactivates

Table 2 ET-1, NO, 8-isoPGF2 α , hs-CRP, and ADMA in hypertensive patients receiving nisoldipine or olmesartan

	Nisoldipine (N = 27) (baseline)	Nisoldipine (N = 23) (8 weeks)	P value	Olmesartan (N = 28) (baseline)	Olmesartan (N = 25) (8 weeks)	P value
ET-1 (pg/mL)	2.18 (1.91–2.56)	1.17 (0.99–1.86)	0.004	2.26 (1.97–3.79)	1.37 (1.00–1.94)	0.001
NO (μ mol/L)	59.3 (31.9–83.3)	63.9 (34.0–100)	0.272	37.9 (19.2–76.6)	46.0 (28.3–65.8)	0.248
8-isoPGF2 α (pg/mL)	35.8 (26.4–42.0)	25.8 (13.0–54.9)	0.879	36.5 (30.4–45.5)	23.0 (14.7–51.4)	0.261
hs-CRP (mg/dL)	1.90 (0.80–4.30) ^a	1.00 (0.60–2.40)	0.012	0.80 (0.45–1.40)	0.70 (0.40–1.45)	0.573
ADMA (ng/mL)	39.4 $\pm$ 13.4	26.8 $\pm$ 11.4	<0.001	40.4 $\pm$ 13.3	29.4 $\pm$ 13.3	<0.001

ET-1, endothelin-1; NO, nitric oxide; 8-isoPGF2 α , 8-isoprostane; hs-CRP, high-sensitive C-reactive protein; ADMA, asymmetric dimethylarginine.

Data are given as mean $\pm$ SD or median (interquartile range) for variables that deviated from normal distribution.

^aP < 0.05 versus the olmesartan group; P value for difference between baseline and 8 weeks later.

endothelium-derived NO, may impair endothelial function. Consistent with the literature [29, 30], we found increased levels of 8-isoPGF2 α , a marker of oxidative stress, in essential hypertensive patients. However, our treatment with nisoldipine or olmesartan failed to cause any apparent reduction in 8-isoPGF2 α levels in the patients, indicating that nisoldipine or olmesartan did not improve endothelial function by militating against oxidative stress in hypertensive subjects. Angiotensin II increases the production of oxygen free radicals, and angiotensin receptor blockade decreases oxidative stress by reducing AT1 receptor activation. It remains likely that a longer period of olmesartan therapy may be required to observe any effect on oxidative stress in hypertensive subjects.

Previous studies have reported that calcium channel blockers [31,32] have antiinflammatory properties. Calcium channel blockers decrease CRP by reducing the production of interleukin-1 and transforming growth factor, avoiding stimulating the production of CRP in hepatic cells. However, antiinflammatory activity of nisoldipine has not been reported. Consistent with previous reports [33,34], we found higher hs-CRP levels in essential hypertensive patients, confirming that inflammation is indeed associated with essential hypertension. We further found that nisoldipine significantly decreased circulating CRP levels, indicating that nisoldipine, similar to other calcium

channel blockers possess antiinflammatory properties. However, we failed to observe any significant antiinflammatory effect by olmesartan.

Methylarginines result from methylation of the arginine residues in proteins by protein arginine methyltransferases (PRMT) using S-adenosylmethionine as a methyl donor. Mild-to-moderate shear stress increased the release of ADMA from human umbilical vein endothelial cells *in vitro* by up-regulating PRMT-I [35]. Increased plasma ADMA levels have been reported for essential hypertensive patients [36,37], which was also observed in the current study. We also found that nisoldipine and olmesartan markedly reduced plasma ADMA levels. We failed to observe any apparent antioxidant activities of nisoldipine and olmesartan, suggesting that nisoldipine and olmesartan lower plasma ADMA levels not by suppressing oxidative stress in hypertensive subjects. On the other hand, we found that nisoldipine and olmesartan therapy was associated with improved FMD, which may lessen shear stress and thus reduce ADMA release. ADMA is an endogenous inhibitor of NO synthase, and reduced plasma ADMA levels might lead to increased NO production and improved endothelial function. However, the plasma levels of NO did not increase significantly in the two treatment groups, and it is possible that oxidative stress might blunt any NO increases [9]. Although NO principally contributes to FMD, endothelium-derived vasoactive substances other than NO (e.g., endothelium-derived hyperpolarizing factor or prostaglandins) also influence FMD [38,39]. Bragulat et al. showed that 6-month irbesartan treatment also improved endothelium-dependent vasodilation without significantly increasing NO production [40].

In conclusion, our study demonstrates that nisoldipine and olmesartan both can significantly decrease plasma ADMA and ET-1 levels and improve FMD. Moreover, nisoldipine has significant antiinflammatory effect. In view of the biological effects of ADMA, ET-1, and CRP on FMD, it suggests that the reductions in plasma ADMA, ET-1, and CRP levels should be, at least in part, favorable for the improvements of FMD. These findings provide clinical evidence for a favorable effect of nisoldipine or olmesartan on endothelium-dependent vasodilation in patients with essential hypertension. Further, larger controlled clinical trials of these agents will be necessary to assess whether these nisoldipine- or olmesartan-induced effects can be translated into an improvement on the cardiovascular endpoints in patients with essential hypertension.

Figure 3 FMD (flow mediated dilation) in hypertensive patients at baseline and 8-week treatment by nisoldipine or olmesartan. Data are given as mean $\pm$ SD. P value for difference between baseline and 8-week later.

Acknowledgments

The authors thank the Shanghai Changfeng Study, which Professor Gao Xin and Doctor Lin Huan-Dong at Department of Endocrinology and Metabolism of Zhongshan Hospital are in charge, for providing many hypertensive patients and normotensive subjects, and Doctor Cui Jie, Cheng Kuan, Lu Hao, Wu Hong-Yi, and Chen Yun-Qin (Department of Cardiovascularology, Zhongshan Hospital) for patients recruitment.

Disclosure

All authors approved to the manuscript, which has not been published before and is not under consideration for publication elsewhere.

Author Contributions

Miss Wei designed the study, developed the study protocol, gained and analyzed data, and wrote the manuscript. Professor Lv provided conceptual oversight over the entire project and interpretation of the results and preparation and revision of the manuscript. Doctor He assisted Miss Wei with the data collection of flow-mediated vasodilation.

Conflict of Interests

The authors have no conflicts of interest to declare.

References

- Landmesser U, Drexler H. Endothelial function and hypertension. *Curr Opin Cardiol* 2007;**22**:316–320.
- Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary artery disease. *Circulation* 2000;**101**:1899–1906.
- Roquer J, Segura T, Serena J, Castillo J. Endothelial dysfunction, vascular disease and stroke: The ARTICO Study. *Cerebrovasc Dis* 2009;**27**:25–37.
- Fang XH, Zhang XH, Yang QD, et al. Subtype hypertension and risk of stroke in middle-aged and older Chinese: A 10-year follow-up study. *Stroke* 2006;**37**:38–43.
- Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA. Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *Circulation* 1993;**87**:1468–1474.
- Shiekh GA, Ayub T, Khan SN, Dar R, Andrabi KI. Reduced nitrate level in individuals with hypertension and diabetes. *J Cardiovasc Dis Res* 2011;**2**:172–176.
- Feletou M, Vanhoutte PM. Endothelial dysfunction: A multifaceted disorder (The Wiggers Award Lecture). *Am J Physiol Heart Circ Physiol* 2006;**291**:H985–1002.
- Böhm F, Ahlborg G, Pernow J. Endothelin-1 inhibits endothelium-dependent vasodilatation in the human forearm: Reversal by ETA receptor blockade in patients with atherosclerosis. *Clin Sci (Lond)* 2002;**102**:321–327.
- Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: The role of oxidant stress. *Circ Res* 2000;**87**:840–844.
- Sibal L, Agarwal SC, Home PD, Boger RH. The role of asymmetric dimethylarginine (ADMA) in endothelial dysfunction and cardiovascular disease. *Curr Cardiol Rev* 2010;**6**:82–90.
- Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. *Circulation* 2002;**106**:1439–1441.
- Benndorf RA, Gehling UM, Appel D, et al. Mobilization of putative high-proliferative-potential endothelial colony-forming cells during antihypertensive treatment in patients with essential hypertension. *Stem Cells Dev* 2007;**16**:329–338.
- Berkels R, Roesen R, Bartels H, et al. Nisoldipine increases the bioavailability of endothelial NO. *Naunyn-Schmiedeberg's Arch Pharmacol* 2001;**364**:110–116.
- Liu JJ, Casley D, Wojta J, et al. Reduction of endothelin levels by the dihydropyridine calcium antagonist nisoldipine and a 'natural factor' in cultured human endothelial cells. *J Hypertens* 1993;**11**:977–982.
- Rosenkranz AC, Lob H, Breitenbach T, Berkels R, Roesen R. Endothelial antioxidant actions of dihydropyridines and angiotensin converting enzyme inhibitors. *Eur J Pharmacol* 2006;**529**:55–62.
- Naya M, Tsukamoto T, Morita K, et al. Olmesartan, but not amlodipine, improves endothelium-dependent coronary dilation in hypertensive patients. *J Am Coll Cardiol* 2007;**50**:1144–1149.
- Takiguchi S, Ayaori M, Uto-Kondo H, et al. Olmesartan improves endothelial function in hypertensive patients: Link with extracellular superoxide dismutase. *Hypertens Res* 2011;**34**:686–692.
- Gao X, Hofman A, Hu Y, et al. The Shanghai Changfeng Study: A community-based prospective cohort study of chronic diseases among middle-aged and elderly: Objectives and design. *Eur J Epidemiol* 2010;**25**:885–893.
- Whitworth JA. World Health Organization International Society of Hypertension Guideline for the management of Hypertension. *J Hypertens* 2003;**21**:1983–1992.
- Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;**39**:257–265.
- Schulze F, Wesemann R, Schwedhelm E, et al. Determination of asymmetric dimethylarginine (ADMA) using a novel ELISA assay. *Clin Chem Lab Med* 2004;**42**:1377–1383.
- Taddei S, Virdis A, Ghiadoni L, Salvetti A. Endothelial dysfunction in hypertension. Fact or fancy? *J Cardiovasc Pharmacol* 1998;**32**(Suppl. 3):S41–S47.
- Nadar S, Blann AD, Lip GY. Endothelial dysfunction: Methods of assessment and application to hypertension. *Curr Pharm Des* 2004;**10**:3591–3605.
- Ohnishi M, Wada A, Tsutamoto T, et al. Endothelin stimulates an endogenous nitric oxide synthase inhibitor, asymmetric dimethylarginine, in experimental heart failure. *Clin Sci (Lond)* 2002;**103**(Suppl. 48):241S–244S.
- Benndorf RA, Appel D, Maas R, Schwedhelm E, Wenzel UO, Böger RH. Telmisartan improves endothelial function in patients with essential hypertension. *J Cardiovasc Pharmacol* 2007;**50**:367–371.
- Morimoto S, Yano Y, Maki K, Sawada K. Renal and vascular protective effects of telmisartan in patients with essential hypertension. *Hypertens Res* 2006;**29**:567–572.
- Shahin Y, Khan JA, Samuel N, Chetter I. Angiotensin converting enzyme inhibitors effect on endothelial dysfunction: A meta-analysis of randomized controlled trials. *Atherosclerosis* 2011;**216**:7–16.
- Hong HJ, Chan P, Liu JC, et al. Angiotensin II induces endothelin-1 gene expression via extracellular signal-regulated kinase pathway in rat aortic smooth muscle cells. *Cardiovasc Res* 2004;**61**:159–168.
- Komiya N, Hirose H, Saisho Y, Saito I, Itoh H. Effects of 12-month valsartan therapy on glycation and oxidative stress markers in type 2 diabetic subjects with hypertension. *Int Heart J* 2008;**49**:681–689.
- Hirooka Y, Kimura Y, Sagara Y, Ito K, Sunagawa K. Effects of valsartan or amlodipine on endothelial function and oxidative stress after one year follow-up in patients with essential hypertension. *Clin Exp Hypertens* 2008;**30**:267–276.
- Komoda H, Inoue T, Node K. Anti-inflammatory properties of azelnidipine, a dihydropyridine-based calcium channel blocker. *Clin Exp Hypertens* 2010;**32**:121–128.
- Ishida S, Koto T, Nagai N, Oike Y. Calcium channel blocker nilvadipine, but not diltiazem, inhibits ocular inflammation in endotoxin-induced uveitis. *Jpn J Ophthalmol* 2010;**54**:594–601.
- Bautista LE, López-Jaramillo P, Vera LM, Casas JP, Otero AP, Guaracao AI. Is C-reactive protein an independent risk factor for essential hypertension. *J Hypertens* 2001;**9**:857–861.
- Wu SL, Gao JS, Hao B, et al. Serum C-reactive protein level is associated with essential hypertension. *Chin J Cardiol* 2003;**31**:917–920.
- Osanaï T, Saitoh M, Sasaki S, Tomita H, Matsunaga T, Okumura K. Effect of shear stress on asymmetric dimethylarginine release from vascular endothelial cells. *Hypertension* 2003;**42**:985–990.
- Perticone F, Sciacqua A, Maio R, et al. Asymmetric dimethylarginine, l-arginine, and endothelial dysfunction in essential hypertension. *J Am Coll Cardiol* 2005;**46**:518–523.
- Pasini AF, Garbin U, Stranieri C, et al. Nebivolol treatment reduces serum levels of asymmetric dimethylarginine and improves endothelial dysfunction in essential hypertensive patients. *Am J Hypertens* 2008;**21**:1251–1257.
- Bellien J, Thuillez C, Joannides R. Contribution of endothelium-derived hyperpolarizing factors to the regulation of vascular tone in humans. *Fundam Clin Pharmacol* 2008;**22**:363–377.
- Sun D, Huang A, Smith CJ, et al. Enhanced release of prostaglandins contributes to flow-induced arteriolar dilatation in eNOS knockout mice. *Circ Res* 1999;**85**:288–293.
- Bragulat E, Larrousse M, Coca A, de la Sierra A. Effect of long-term irbesartan treatment on endothelium-dependent vasodilation in essential hypertensive patients. *Br J Biomed Sci* 2003;**60**:191–196.