Original Article

Beneficial Effects of Combination Therapy with Angiotensin II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor on Vascular Endothelial Function

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The combination of angiotensin I–converting enzyme inhibitors and angiotensin receptor blockers has been shown to be more effective than the individual drugs alone in the treatment of chronic kidney disease and chronic heart failure. In the present study, we evaluated the effect of treatment with the calcium channel blocker amlodipine or the angiotensin I–converting enzyme inhibitor perindopril on vascular endothelial function and arteriosclerosis in patients with essential hypertension who had already been receiving angiotensin receptor blocker monotherapy. Thirty-two patients with essential hypertension treated with angiotensin receptor blocker monotherapy were randomized to receive 5 mg of amlodipine (*n*=16) or 4 mg of perindopril (*n*=16) once daily in the morning for 24 weeks. The patients were evaluated before and after therapy to assess changes in blood pressure, flow-mediated vasodilation (a parameter of vascular endothelial function), and brachial-ankle pulse wave velocity (a parameter of arteriosclerosis). Before treatment, there were no significant differences in the above parameters between groups. After treatment, there was a similar significant decrease in blood pressure in both groups. Flow-mediated vasodilation increased significantly in the perindopril group compared with the amlodipine group; however, the decrease in brachial-ankle pulse wave velocity was not significantly different between groups. In conclusion, these results suggest that the angiotensin I–converting enzyme inhibitor perindopril is superior to the calcium channel blocker amlodipine for reducing vascular endothelial dysfunction when co-administered with angiotensin receptor blockers in patients with essential hypertension. (*Hypertens Res* 2008; 31: 1603–1610)

***Key Words*: essential hypertension, angiotensin I–converting enzyme inhibitor, angiotensin receptor blocker, calcium antagonist, vascular endothelial dysfunction**

Introduction

Antihypertensive therapy is used for the prevention of cardiovascular disease morbidity and, ultimately, mortality resulting from heart and blood vessel dysfunction triggered by constant hypertension. Although the prevailing opinion has long been that the protective effect of all classes of drugs against cardiovascular mortality is the same (with equal degrees of blood pressure [BP] reduction), recent trials prove the opposite. Each class, and even each drug in a specific class, may have a specific organ-protective effect. In addition, specific drug combinations should provide maximal antihypertensive action as well as maximal organ-protective

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Table 1. Patient Characteristics

	A Group (n=16)	P Group (n=16)
Age (years)	65±2	63±3
Sex (male/female)	7/9	8/8
Family history of hypertension (yes/no)	9/7	10/6
History of hypertension (years)	7±2	8±1
Smoking (yes/no)	4/12	3/13
Body mass index (kg/m^2)	23.9±1.4	24.2±1.8
Systolic blood pressure (mmHg)	146±4	145±2
Diastolic blood pressure (mmHg)	83±3	81±3
Heart rate (bpm)	70±2	73±3
Fasting glucose (mg/dL)	116±5	109±9
HbA1c (%)	5.3±0.1	5.6±0.2
LDL cholesterol (mg/dL)	132±12	138±13
Triglyceride (mg/dL)	158±24	164±18
HDL cholesterol (mg/dL)	63± 4	60± 4
Blood urea nitrogen (mg/dL)	19.5±3.2	20.0±2.9
Serum creatinine (mg/dL)	0.7±0.4	0.7±0.2
Baseline diameter of the brachial artery (mm)	4.0±0.3	4.0±0.2
%FMD (%)	3.0±0.6	2.7±0.8
%NMD (%)	10.1±1.1	9.4±1.1
Endothelial function index (%)	29.7±8.2	28.7±9.9
baPWV (cm/s)	1,624±64	1,650±59

Values are expressed as the mean±SEM. A, amlodipine; P, perindopril; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation; baPWV, brachial-ankle pulse wave velocity.

effects. The combination of angiotensin I–converting enzyme inhibitors (ACE-I) and an angiotensin II receptor blocker (ARB) has been shown to be more effective than the individual drugs alone in the treatment of microalbuminuria diabetes (*1*), diabetic nephropathy (*2*, *3*), and non-diabetic nephropathy (*4–8*). In chronic heart failure, this combination therapy reduces the combined endpoint of mortality and morbidity compared with monotherapy (*9*, *10*).

Vascular endothelial dysfunction and arteriosclerosis are caused by hypertension, and they are also risk factors for cardiovascular events. Therefore, therapeutic strategies to reduce endothelial dysfunction and arteriosclerosis are required. Several lines of evidence indicate that ACE-Is and ARBs reduce vascular endothelial dysfunction (*11–15*) and arteriosclerosis (*15*, *16*). Beneficial effects of combination therapy with ACE-I and ARB on endothelial dysfunction have been reported in animal models (*17*) but not in humans.

In the present study, we evaluated the effect of treatment with the calcium channel blocker (CCB) amlodipine or the ACE-I perindopril on vascular endothelial function and arteriosclerosis in patients with essential hypertension who had already been treated with an ARB.

Table 2. Medications at Baseline

	A Group (n=16)	P Group (n=16)
ARB		
Losartan (25–50 mg)	3	4
Candesartan (8 mg)	5	5
Valsartan (80 mg)	3	3
Telmisartan (20–40 mg)	5	4
Anti-diabetic drugs	1	2
Anti-hyperlipidemic drugs	4	3
Anti-platelet drugs	1	1

A, amlodipine; P, perindopril; ARB, angiotensin receptor blocker.

Methods

Study Subjects

The subjects were selected from among essential hypertensives with BP remaining at 140/90 mmHg or higher after receiving ARB monotherapy who visited our center between April 2003 and January 2005. Patients who had ischemic heart disease, acute coronary syndrome, congestive heart failure (New York Heart Association class II or greater), or stroke within 6 months of study initiation, impaired renal function (serum creatinine: ≥1.5 mg/dL), or were pregnant were excluded. Included patients were randomly divided into two groups according to birth year and co-prescribed either amlodipine (even-numbered year, 5 mg/d, once daily in the morning, A group) or perindopril (uneven-numbered year, 4 mg/d, once daily in the morning, P group) for 24 weeks in addition to their existing therapy. During this study, additional treatment or dosage changes for concomitantly administered anti-hyperlipidemic, anti-diabetic, or anti-platelet drugs were prohibited.

Measurements

Parameters were measured at baseline and after 24 weeks of treatment.

BP/Heart Rate

Measurements of outpatient BP and heart rate (HR) were obtained twice in the sitting position after 2 to 3 min of rest at 2 to 5 h after administration of the test drug, and the mean of the two values was determined.

Vasodilation

Endothelium-dependent and -independent dilations were assessed as parameters of vasodilation according to the guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery (*18*). Using

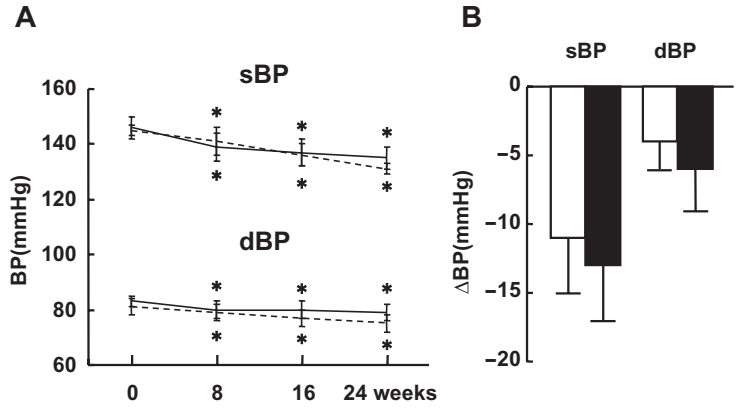

Fig. 1. *A: Time course of blood pressure changes during treatment with amlodipine or perindopril. Solid line, amlodipine group; dotted line, perindopril group. B: Blood pressure changes by amlodipine or perindopril 24 weeks after treatment. Open bar, amlodipine group; closed bar, perindopril group. sBP, systolic blood pressure; dBP, diastolic blood pressure. n = 16 for both groups. *p < 0.05 compared with before treatment.*

a high-resolution ultrasound (Logiq 500; GE Yokogawa Medical Systems, Tokyo, Japan) with a 7.5-MHz linear array transducer, diameter measurements of the brachial artery were taken after supine rest for at least 5 min, and, after cuff deflation, suprasystolic compression (30 mmHg above systolic pressure) was performed at the upper arm for 2 min and, again, after patients received sublingual nitroglycerin 0.3 mg. A stereotactic arm was used for optimal transducer positioning on the brachial artery proximal to the bifurcation of the radial and ulnar arteries. The longitudinal image of the artery was recorded at baseline, continuously from 30 s before to 2 min after cuff deflation, and for 5 min after nitroglycerin administration. The diameter of the artery was measured from one media-adventitia interface to the other. The maximum vasodilation was then evaluated from the change in artery diameter after release of occlusion (%FMD) and after administration of nitroglycerin (%NMD). The ratio of %FMD/%NMD was calculated as the endothelial function index to estimate the vasodilatory function more specifically to the endothelial function (*19*).

Arterial Stiffness

The brachial-ankle pulse wave velocity (baPWV) was measured bilaterally using a volume-plethysmographic PWV/ABI device (Omron Healthcare Co., Ltd, Kyoto, Japan) in accordance with methodology described elsewhere (*20*, *21*), and the mean value was calculated to provide a parameter of arteriosclerosis.

Statistics

The data were analyzed by the paired or unpaired Student's *t*-test to detect significant differences before and after treatment or between groups, respectively. Values are shown as the means±SEM, and differences were considered statistically significant at $p<0.05$.

This study was approved by the Ethical Committee of Ohmihachiman City Hospital. Before enrollment, the subjects were given complete information about the study and their consent was obtained.

Results

The study comprised 32 patients (15 men and 17 women), with 16 assigned to the A group and 16 assigned to the P group. There were no differences in baseline characteristics, such as sex, age, smoking status, body mass index, or biochemical parameters, between the two groups (Table 1). The number of patients taking ARB, anti-hyperlipidemic drugs, anti-diabetic drugs, and anti-platelet drugs was not significantly different between groups (Table 2).

No subjects changed their smoking status during the study period. Body mass index (23.8±1.4 kg/m^2 in the A group and 24.3±1.7 kg/m^2 in the P group after treatment), fasting glucose (113±7; 110±12 mg/dL), hemoglobin A1c (5.2±0.2; 5.5±0.3%), low-density lipoprotein (LDL) cholesterol (134±14; 136±13 mg/dL), triglyceride (155±34; 160±23 mg/dL), high-density lipoprotein (HDL) cholesterol (65±6; 62±9 mg/dL), blood urea nitrogen (19.3±4.2; 20.2±3.6 mg/dL), and serum creatinine (0.7±0.3; 0.7±0.2 mg/dL) did not change in either group. Furthermore, there were no differences in these values between groups.

BP/HR

There was no difference in baseline BP between the two groups (Table 1). After the start of treatment, BP showed a similar gradual and significant decrease with time in both groups (Fig. 1A). After 24 weeks of treatment, BP was 135±4/79±3 mmHg in the A group and 131±2/75±3 mmHg in the P group, and there was no between-group difference in

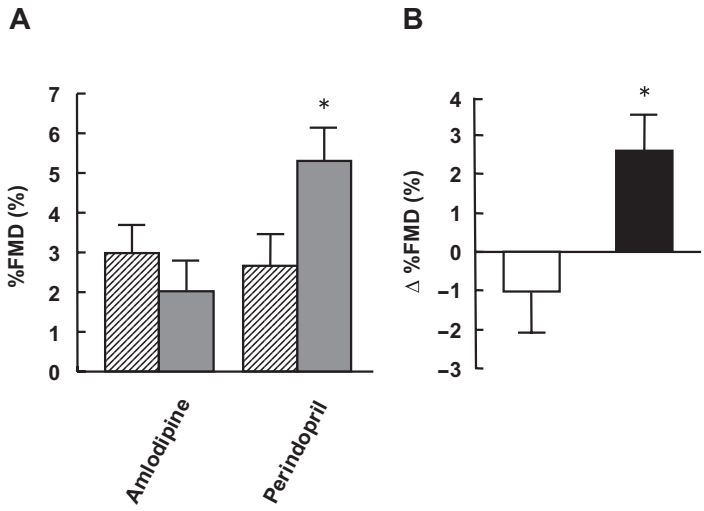

Fig. 2. *Effect of amlodipine and perindopril on flow-mediated dilatation. Hatched bars, before treatment; gray bars, after treatment; open bar, amlodipine group; closed bar, perindopril group. FMD, flow-mediated dilatation. n = 16 for both groups. *p < 0.05 compared with before treatment.*

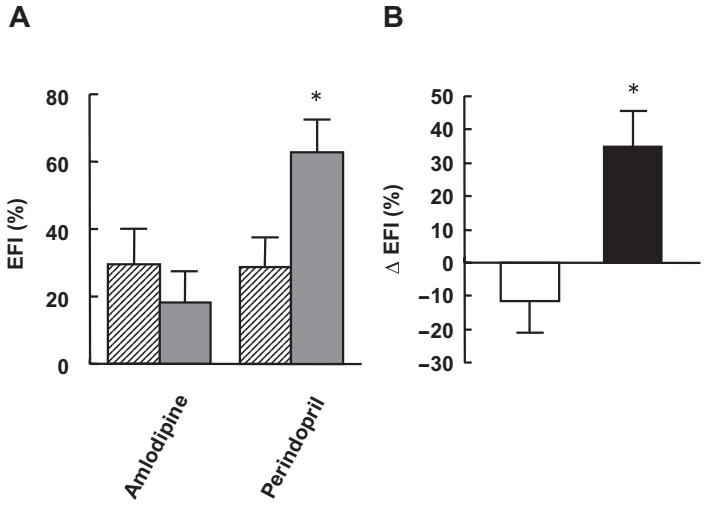

Fig. 3. *Effect of amlodipine and perindopril on endothelial function index. Hatched bars, before treatment; gray bars, after treatment; open bar, amlodipine group; closed bar, perindopril group. n = 16 for both groups. *p < 0.05 compared with before treatment.*

this change (Fig. 1B). There was no difference in baseline HR between the two groups (Table 1), HR did not change significantly in either group (71±3 bpm in the A group and 72±3 bpm in the P group after the treatment), and there was no difference in the change in HR between the two groups.

Vasodilation

The baseline diameter was not significantly different between the two groups (Table 1). There were no differences in baseline %FMD, %NMD, or endothelial function index between the two groups (Table 1). %FMD significantly increased following treatment in the P group (5.2±0.9% after treatment) but not in the A group (2.0±0.8%) (Fig. 2A). The P group showed a significantly greater increase in %FMD than the A group (Fig. 2B). However, %NMD did not change significantly in either group (10.9±1.4% in the A group and 8.3±1.3% in the P group after treatment). There were no differences in the degree of change between the two groups. The endothelial function index significantly increased following treatment in the P group (62.7±9.7% after treatment) but not in the A group (18.3±8.8%) (Fig. 3A). The P group showed a

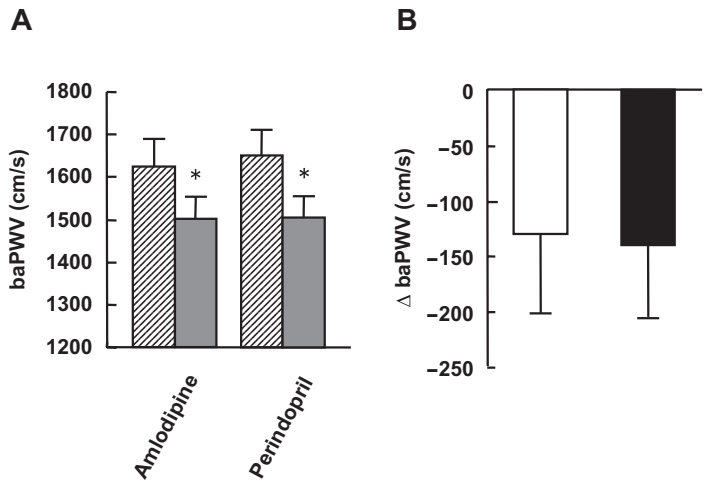

Fig. 4. *Effect of amlodipine and perindopril on the brachial-ankle pulse wave velocity. Hatched bars, before treatment; gray bars, after treatment; open bar, amlodipine group; closed bar, perindopril group. baPWV, brachial-ankle pulse wave velocity. n = 16 for both groups. *p < 0.05 compared with before treatment.*

significantly greater increase in the endothelial function index than the A group (Fig. 3B).

Arterial Stiffness

There was no difference in baseline baPWV between the two groups (Table 1). Although baPWV showed a significant decrease after treatment in both groups (1,504±53 cm/s in the A group and 1,508±50 cm/s in the P group) (Fig. 4A), the changes were not significantly different between groups (Fig. 4B).

Discussion

The goal of antihypertensive therapy is to prevent cardiovascular complications; thus, the organ-protective effects of antihypertensive drugs are very important. This study was conducted to compare the vascular protective effects of combination therapy with ARB and CCB, and ARB and ACE-I in patients with essential hypertension. Both therapeutic regimens exhibited similar antihypertensive effects. Factors that might be expected to alter vascular function, such as smoking status, body mass index, fasting glucose, hemoglobin A1c, and lipid levels, did not change during the study period. Nevertheless, ARB/ACE-I combination therapy markedly improved vascular endothelial function compared with ARB/CCB combination therapy.

The combination of ARB and ACE-I has already been proposed as a method to obtain a more complete blockade. Because ARB and ACE-I interfere with the renin-angiotensin system in a different way, it was suggested that this combination should preserve the benefits of bradykinin potentiation offered by ACE-I while providing potential antitrophic influences of angiotensin II type 2 receptor stimulation with an ARB (*22*, *23*). Although there were some initial concerns regarding the use of such combinations, this combination is currently considered to be a rational choice for selected patients because of the complementary actions of these drugs (*24*, *25*).

Animal studies have provided solid evidence that such a class combination is more beneficial than monotherapy (*26*). The beneficial effect of such a combination on blood flow has been shown in different animal models (*27*, *28*), and effects on bradykinin and nitric oxide production have been suggested (*29*, *30*).

The vascular endothelium releases various vasoactive substances that exhibit vasoprotective effects (*31*, *32*). Given that endothelial damage is known to activate smooth muscle cells and to cause intimal hypertrophy, which, in turn, leads to arteriosclerosis (*33*), the effect of antihypertensive drugs on vascular endothelial function is important. Several lines of evidence indicate that monotherapy with ACE-I, ARB, or the CCB reduces vascular endothelial dysfunction (*15*, *34–36*) and arteriosclerosis (*15*, *16*). Furthermore, beneficial effects of combination therapy with ACE-I and ARB on endothelial dysfunction have been reported in animal models (*17*). However, a beneficial effect has not been shown in humans. Combination therapy with ARB and CCB is now widely used in the treatment of hypertension (*37*). Therefore, in the present study, we compared the effects of an ACE-I or a CCB in addition to ARB therapy on changes in flow-mediated dilation, which is a non-invasive test for measuring peripheral endothelial function (*38*) that correlates with cardiovascular risk factors (*38–42*) and coronary endothelial function (*43*). The combination therapy did not lead to significant modification of systolic and diastolic BP or HR. In contrast, %FMD and

endothelial function index, but not %NMD, endothelium-independent dilation, was significantly greater in patients receiving ARB/ACE-I combination therapy than those receiving ARB/CCB combination therapy. Therefore, we propose that ACE-I has stronger endothelium-protecting effects than CCB when co-administered with an ARB. Whether ARB/ACE-I combination therapy is superior to a double dose of ARB monotherapy remains unclear because only few studies have compared these regimens. Ogawa *et al*. (*44*) reported that the combination of ARB and ACE-I has renoprotective effects similar to double-dose ARB in diabetic nephropathy (*44*). Similar studies comparing the effects of these regimens on vascular endothelial dysfunction are required to address this issue.

Pulse wave velocity (PWV) is an index of arterial stiffness (*45*) and is regarded as a non-invasive marker of vascular damage (*46–48*). A recent study demonstrated that the association of perindopril with the ARB valsartan shows significantly greater reduction in baPWV compared with each as monotherapy in patients with essential hypertension (*49*). Unexpectedly, decreases in baPWV were not significantly different between treatment with CCB and ACE-I co-administered with an ARB in the present study. The reason for this discrepancy is unclear. In addition, the reason why the ARB/ACE-I combination therapy exhibited a significantly greater improvement in %FMD and endothelial function index but not baPWV compared with ARB/CCB combination therapy remains to be determined. This finding could be due to the different beneficial effects of CCBs on endothelial dysfunction and atherosclerosis. Greater inhibition of atherosclerosis or cardiovascular events by CCB than ACE-I (*50*) has been reported while stronger improvement of endothelial dysfunction by ACE-I than CCB has also been reported (*14*). This assumption, however, remains speculative, and further studies are needed to address this issue.

Our data may contrast with the findings from the recently reported "Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial" (ONTARGET), which failed to indicate additional advantage from the combination of the ARB telmisartan and ACE-I ramipril as compared with ramipril alone in preventing death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure (*51*). The reason for the discrepancy remains unclear; however, differences in the study design may provide some explanations for this discrepancy. These study design differences include: 1) the ONTARGET compared ACE-I/ARB and ACE-I while our study compared ARB/ACE-I and ARB/CCB, 2) the ONTARGET used full doses of ACE-I and ARB (leading to the presumption that the full dose of ACE-I was too effective for the ARB to show additive organ protective effects) while our study used regular doses or smaller doses of ACE-I and ARB, and 3) the ONTARGET was done in patients at high risk for vascular events while our study was performed in patients with essential hypertension.

In conclusion, the results of this study show that the ACE-I perindopril is similar to the CCB amlodipine in terms of antihypertensive action but is superior in terms of improving vascular endothelial dysfunction when co-administered with ARBs in patients with essential hypertension. Although the trial enrolled only 32 patients and lasted only 6 months, it mimics common clinical settings, and, since beneficial effects were observed, the prescription of perindopril in patients already treated with ARBs may be the treatment of choice. However, whether the present results are specific to perindopril or common to all ACE-Is remains to be determined. In addition, the present study has several limitations in regards to the methodology and interpretation of the results of the vasodilation tests. These limitations include: 1) hyperemic blood flow was not measured, 2) the dose of nitroglycerin used might be too high because %NMD was much larger when compared with %FMD, and 3) it is difficult to determine whether the effects of perindopril on endothelial function were BP-independent because the antihypertensive effects in both groups were not exactly the same. Further studies investigating the effects of combination therapy with other ACE-Is and ARBs are needed to address or resolve these issues. In addition, further investigations are required to determine the underlying mechanisms by which the combination therapy achieves its beneficial effects.

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