Original Article

Telmisartan, an Angiotensin II Type 1 Receptor Blocker, Improves Coronary Microcirculation and Insulin Resistance among Essential Hypertensive Patients without Left Ventricular Hypertrophy

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Hypertension and insulin resistance are associated with reduced coronary vasodilatory capacity, possibly caused by structural changes in the coronary resistance vessels. The goal of this study was to compare the effect of an angiotensin receptor blocker (ARB) with that of a calcium channel blocker (CCB) on coronary flow reserve and insulin resistance among essential hypertensive patients without left ventricular hypertrophy. A total of 40 consecutive essential hypertensive patients were randomized to daily 40 mg telmisartan or 20 mg nifedipine coat-core treatment. Coronary flow velocity reserve (CFVR) measurement using transthoracic Doppler echocardiography and blood tests were performed before and after 12 weeks of treatment. At baseline, blood pressure, CFVR, and homeostasis model assessment of insulin resistance (HOMA-IR) were not significantly different between the two groups. At the end of the treatment period, the telmisartan and nifedipine groups exhibited similar declines in blood pressure. CFVR was improved in the telmisartan group (2.4±0.4 to 2.9±0.4; $p<0.01$), but there was no difference in the nifedipine group (2.5±0.3 to 2.5±0.3; n.s.). HOMA-IR was improved in the telmisartan group (3.1±1.1 to 1.6±0.7; $p<0.01$), but there was no difference in the nifedipine group (2.8±1.1 to 2.4±0.7; n.s.). In conclusion, this study demonstrates that antihypertensive therapy with telmisartan, but not nifedipine, has a beneficial effect on coronary microcirculation and insulin resistance among essential hypertensive patients. (*Hypertens Res* 2008; 31: 615–622)

***Key Words*: hypertension, angiotensin receptor blocker, coronary circulation, insulin resistance, Doppler echocardiography**

Introduction

Coronary flow reserve (CFR) is considered an important physiologic parameter in the coronary circulation, reflecting the function of large epicardial arteries and the microcirculation. Recently, several reports have shown that epicardial coronary blood flow velocity can be measured by transthoracic Doppler echocardiography (TTDE), a non-invasive test in wide clinical use (*1*). In patients with arterial hypertension, CFR is impaired because of functional and structural alterations of the coronary microcirculation and left ventricular hypertrophy (LVH) (*2*, *3*). It has also been reported that maximal myocardial vasodilatory capacity is reduced in patients with diabetes mellitus (*4*, *5*). The purpose of this study was to compare the effects of antihypertensive treatment in which telmisartan, an angiotensin receptor blocker (ARB), is given with nifedipine, a calcium channel blocker (CCB), on coronary microcirculation and insulin resistance in patients with essential hypertension, and to investigate the so-called

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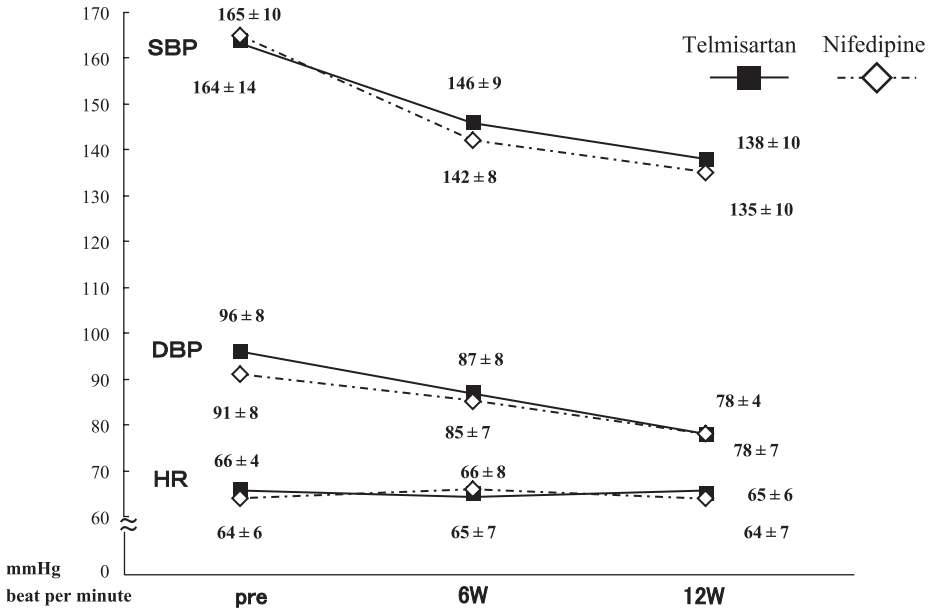

Fig. 1. *Time course of blood pressure and heart rate changes by treatment with nifedipine or telmisartan. Dotted line, nifedipine group; solid line, telmisartan group; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.*

"beyond blood pressure–lowering effect" of ARBs.

Methods

Subjects

We randomized a total of 40 consecutive outpatients (18 males and 22 females) newly diagnosed with mild to moderate essential hypertension (diastolic blood pressure, 90–109 mmHg; systolic blood pressure, 140–179 mmHg [mean of 3 different measurements on 3 different visits]) with no clinical signs of irreversible target organ damage (World Health Organization I/II) to a double-blind parallel group comparison of treatment with either telmisartan or nifedipine. None of the subjects had a history of treatment for hypertension at the time of enrollment in the study. Exclusion criteria were secondary forms of arterial hypertension, previous myocardial infarction, angina pectoris, coronary bypass surgery, coronary angioplasty, stroke or transient ischemic attack within 12 months, congestive heart failure, cardiac arrhythmia, impaired renal function, diagnosed diabetes mellitus, valvular heart disease, and abnormal echocardiograms. Using these criteria, all the subjects were assigned to receive 12 weeks of treatment with 40 mg telmisartan (Boehringer Ingelheim Pharma, Ingelheim, Germany) or 20 mg nifedipine coat-core (Bayer Health Care, Leverkusen, Germany) once daily in the morning.

None of the patients had any symptoms of coronary artery disease, and all had negative findings on maximum exercise–stress electrocardiograph.

Laboratory analysis and measurement of coronary flow velocity reserve (CFVR) were performed at the time of enrollment and after 12 weeks of treatment. During their visit to the hospital after enrollment, the patients were given adequate advice with which to improve their lifestyles, including eating habits and the importance of frequent exercise.

All subjects were aware of the experimental procedure and gave written informed consent. The study was approved by the Ethics Committee of the Kure Kyosai Hospital and was performed in accordance with the Declaration of Helsinki.

Echocardiographic Examinations

Echocardiographic examinations were performed with a Vivid digital ultrasound system 3 (GE Medical Systems, Milwaukee, USA) equipped with a 2.5 to 7.5 MHz phased-array transducer. All patients underwent two-dimensional echocardiography. M-mode tracing and Doppler signals were recorded and the measurements taken using the standard methods. Using a frequency range of 7.5–10 MHz, the spectral Doppler signals at rest were first recorded in the distal portion of the left anterior descending artery. To obtain the apparent Doppler image, we used a microbubble-based ultrasonographic contrast agent, 300 mg/mL of Levovist (Schering Japan, Osaka, Japan). Adenosine was administered (140 μg/kg/min) for 5 min to record spectral Doppler signals during hyperemic conditions. The time-averaged peak diastolic flow velocity (APDV) was determined from the traced area of the three continuous diastolic flow velocity signals. APDV was measured at rest and under hyperemic conditions upon enrollment and after 12 weeks of antihypertensive treatment. CFVR was defined as the ratio of hyperemia to rest APDV.

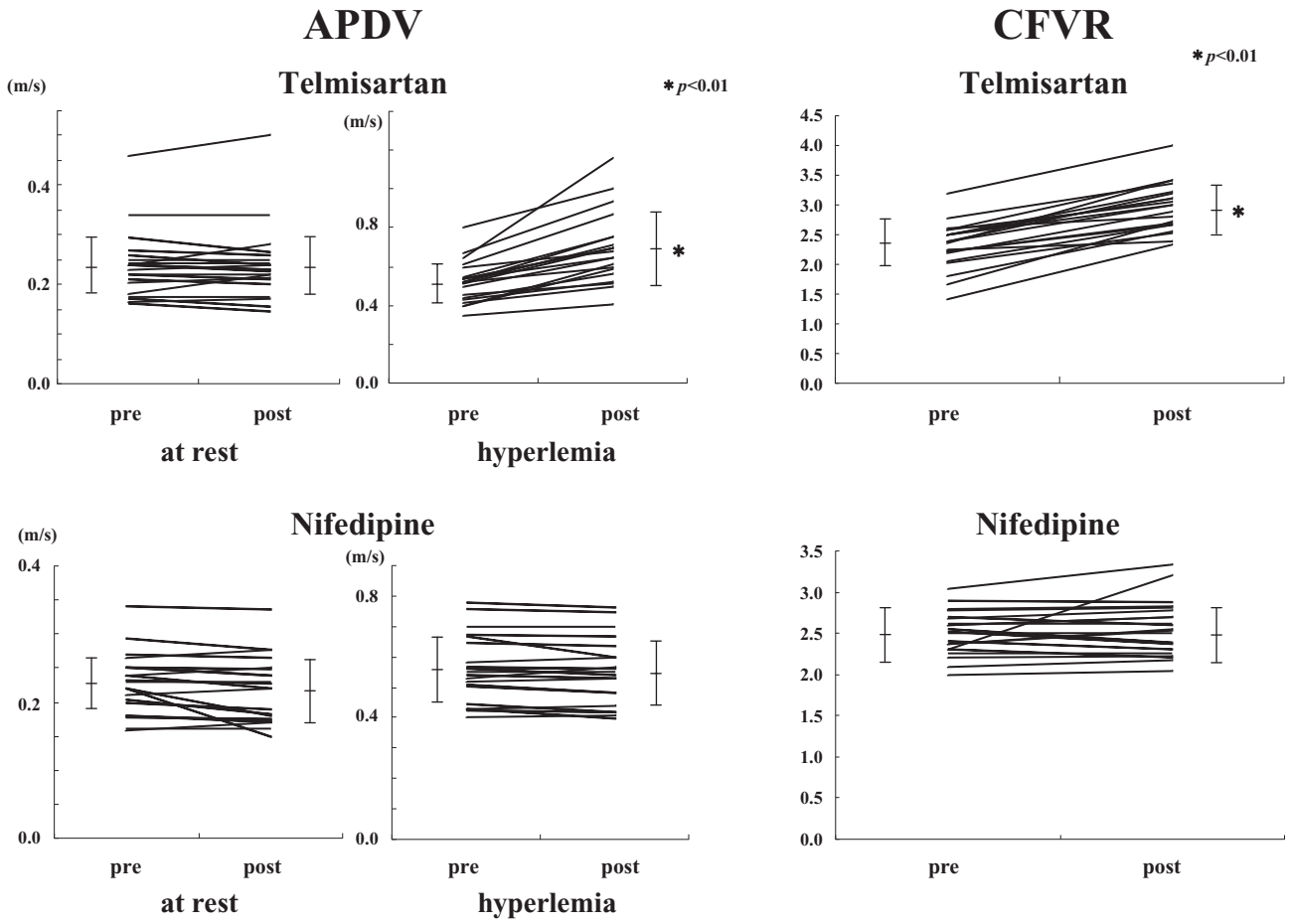

Fig. 2. *Changes in coronary circulation before and after 12 weeks of treatment. Upper panels show the telmisartan group. Lower panels show the nifedipine group. Left panels show average peak diastolic velocity (APDV). Right panels show coronary flow velocity reserve (CFVR). Before treatment (left dot) and after (right dot). *p < 0.01, compared with before treatment.*

Each measurement was analyzed by two experienced investigators who were unaware of other patient data, including the treatment regimen. Inter-observer and intra-observer variability for quantitative Doppler velocity measurements was assessed in 10 randomly selected patients.

Laboratory Analysis

The blood tests were performed under overnight fasting conditions of more than 12 h. A TBA80 auto-analyzer (Toshiba, Tokyo, Japan) was used to determine serum concentrations of fasting plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein-cholesterol by enzymatic methods. The plasma insulin concentration was determined by radioimmunoassay (SRL, Tokyo, Japan), and insulin resistance was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR), defined by the following formula: (fasting plasma insulin [μU/mL] × fasting plasma glucose [mmol/L])/22.5.

Statistical Analysis

Mean values±SDs are expressed for the parametric data. Baseline characteristics were compared by the Fisher's exact or Cochran-Mantel-Haenszel tests. Analysis of variance was used to test the treatment group for baseline differences in continuous variables. The hemodynamic response to various antihypertensive agents was compared by parametric analysis of covariance, with the baseline level used as the covariate. Within-treatment analysis of changes was performed at the 0.05 significance level with Student's *t*-test. The relationship between changes in CFVR and changes in HOMA-IR was assessed using the Pearson correlation coefficient. A p value of <0.05 was considered significant. Statistical analyses were performed by SPSS 11.0 J for Windows (SPSS, Chicago, USA).

Table 1. Patient Baseline Characteristic (n=40)

	Telmisartan (n=20)	Nifedipine (n=20)	p value
Age (years old)	62±7	63±8	n.s.
Male/female	8/12	9/11	n.s.
Body mass index	24±1.5	23±1.2	n.s.
Smoker (n (%))	2 (10%)	2 (10%)	n.s.
Total cholesterol (mmol/L)	5.1±0.4	5.0±0.3	n.s.
Triglycerides (mmol/L)	1.9±0.2	1.9±0.2	n.s.
High-density lipoprotein cholesterol (mmol/L)	1.1±0.2	1.2±0.2	n.s.
Fasting plasma glucose (mmol/L)	5.6±0.5	5.6±0.4	n.s.
Left ventricular diastolic diameter (mm)	46±4.1	46±4.1	n.s.
Left ventricular systolic diameter (mm)	27±3.6	27±3.7	n.s.
Interventricular septum (mm)	11±1.1	10±1.5	n.s.
Left ventricular posterior wall (mm)	10±1.1	9.6±1.2	n.s.
Ejection fruction (%)	73±5	71±5	n.s.
E/A	0.8±0.2	0.9±0.2	n.s.

Results

Study Population and Laboratory Findings

One patient, who had severe emphysema, could not be enrolled in the present study because of poor echo examination results.

Age and gender distributions as well as the number of previously treated patients in each group were similar, and the baseline characteristics of the 40 patients who underwent randomization were similar in both groups, including lipid profiles, glucose profiles, and ultrasound echocardiographic findings.

The study was completed by all 20 patients in both groups. None of the patients withdrew from the study. There were no major or minor cardiovascular events in either group.

Changes in Blood Pressure and Heart Rate

Blood pressure was controlled for a mean duration of 11±1 weeks. Pretreatment systolic and diastolic blood pressures were similar in both groups. The effects of both antihypertensive agents were satisfactory. The changes in systolic and diastolic blood pressures and heart rate were not significantly different between the two groups (Fig. 1).

Changes in Coronary Circulation

Pretreatment averaged peak diastolic velocity (APDV) at rest and under hyperemic conditions was not different between the telmisartan and nifedipine groups (0.24±0.6 and 0.23±0.4 m/s, respectively, n.s.; 0.52±0.1 and 0.56±0.1 m/s, respectively, n.s.). After 12 weeks of drug treatment, there was no significant change in APDV at rest, but APVD under hyperemic conditions (0.52±0.1 to 0.70±0.2 m/s, p<0.01) and CFVR improved in the telmisartan group (2.4±0.3 to 2.9±0.4 m/s; p<0.01); there was no difference in the nifedipine group (2.5±0.3 to 2.5±0.3 m/s; p=0.8; Fig. 2).

Changes in Glucose and Lipid Profiles

There were no significant differences between the two groups in the concentration of fasting blood glucose, fasting insulin, and HOMA-IR before treatment (Table 1). There was no significant change in the concentration of fasting plasma glucose before and after treatment in either group (5.7±0.4 to 5.7±0.4 mmol/L; respectively, n.s.). After treatment, the concentration of plasma fasting insulin was improved in the telmisartan group (12±6 to 7±3 μU/mL; p<0.01) but not in the nifedipine group (11±5.6 to 10±6.0 μU/mL; p=0.57). The HOMA-IR was improved in the telmisartan group (3.1±1.1 to 1.6±0.7; p<0.01), but there was no difference in the nifedipine group (2.8±1.1 to 2.4±0.7; n.s.; Fig. 3).

There was no statistical change in the lipid profile in both treatments (data not shown).

Relationship between Changes in Coronary Microcirculation and Insulin Resistance

In the telmisartan group, a significant inverse relationship was recognized between changes in HOMA-IR and CFVR (y= −0.976x − 13.5, r^2=0.81; p<0.01) (Fig. 4).

Discussion

The principal finding of this study was that a 12-week oral administration of an ARB, but not that of a CCB, improved CFVR and insulin resistance among patients with essential hypertension.

The difference in CFVR occurred despite a similar decline in blood pressure with both agents. These results suggest that

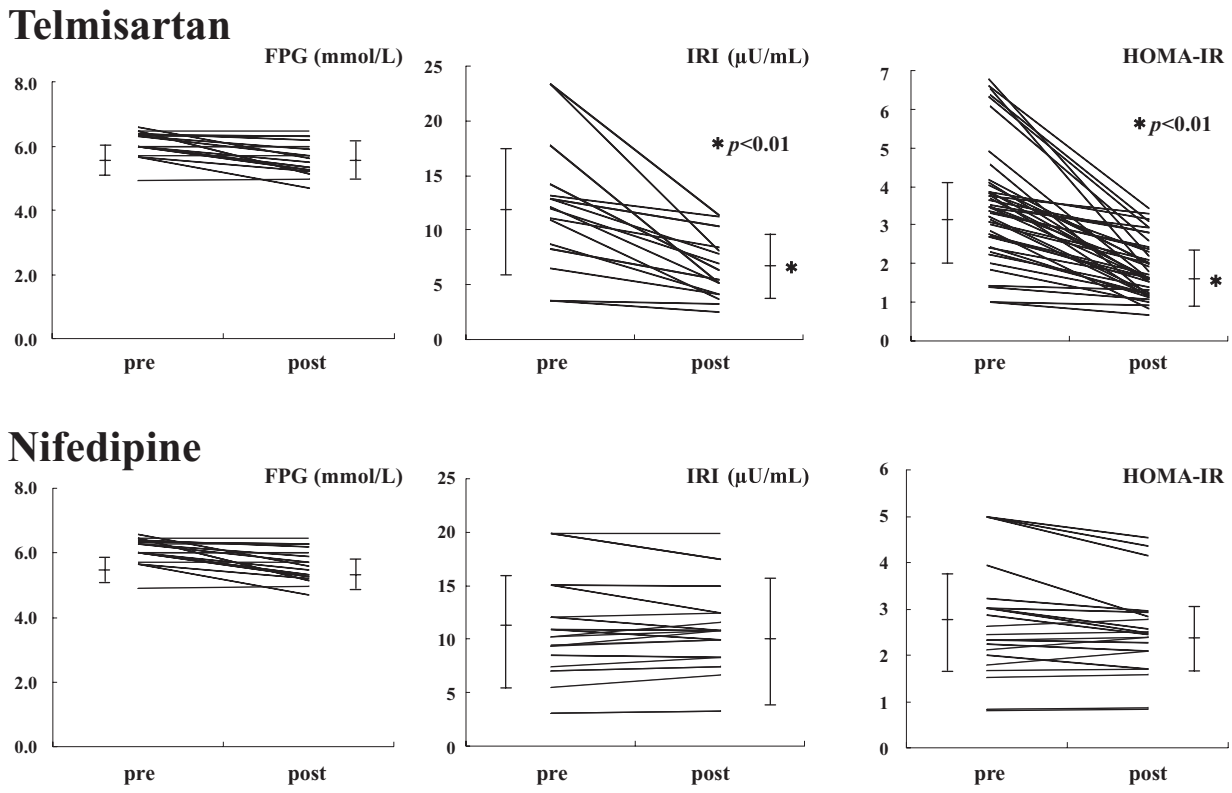

Fig. 3. *Changes in glucose metabolism before and after 12 weeks of treatment. Fasting plasma glucose (FPG; left); fasting plasma insulin (IRI; middle), and HOMA-IR (right). Upper: telmisartan group. Lower: nifedipine group. Before treatment (left dot) and after (right dot). *p < 0.01, compared with before treatment.*

ARBs may have favorable effects on coronary circulation in essential hypertension patients beyond the ability to lower blood pressure, as compared with CCBs.

To the best of our knowledge, this is the first report that shows a beneficial effect of ARBs on coronary circulation among patients with essential hypertension without left ventricular hypertrophy.

The Renin-Angiotensin System and Coronary Circulation

The renin-angiotensin system (RAS) is an important regulator of blood pressure and body fluid homeostasis in healthy individuals. The RAS system also plays a primary role in modulating vascular structure and function by a variety of mechanisms (*6*).

The RAS plays an important role in increasing arterial pressure and regulating cardiovascular function in patients with hypertension. However, the impact of the RAS on hypertension extends beyond the increase in arterial pressure to encompass several aspects of hypertensive heart disease (HHD), including LVH, coronary insufficiency, endothelial dysfunction, and occlusive coronary artery disease (*7*, *8*).

It was previously reported that a significant reduction in CFR is already detectable and related to an impaired coronary vasodilator capacity in hypertensive patients (*3*).

Several basic and clinical reports have demonstrated that antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor can improve the diminished coronary reserve in patients with arterial hypertensive heart disease. In animal trials, Kitakaze *et al*. (*9*) reported that infusion of ARB into canine coronary arteries caused an increase in coronary blood flow, and that the combination of an ACE inhibitor and an ARB mediated a greater increase in coronary blood flow. They argued that an ARB could enhance ACE inhibitor–induced NO production.

Motz *et al*. (*10*) reported that 12 months of therapy with enalapril using a gas chromatographic argon method improved human CFR. Schwartzkopff *et al*. (*11*) also reported that long-term therapy with the ACE inhibitor perindopril by an inert chromatographic argon method induced the improvement of CFR, and they observed the structural repair of coronary arterioles through transvenous endomyocardial biopsies.

Using positron emission tomography, Akinboboye *et al*. (*12*) found that myocardial perfusion reserve and absolute hyperemic myocardial blood flow improved in patients with hypertension-induced LVH after long-term treatment with the

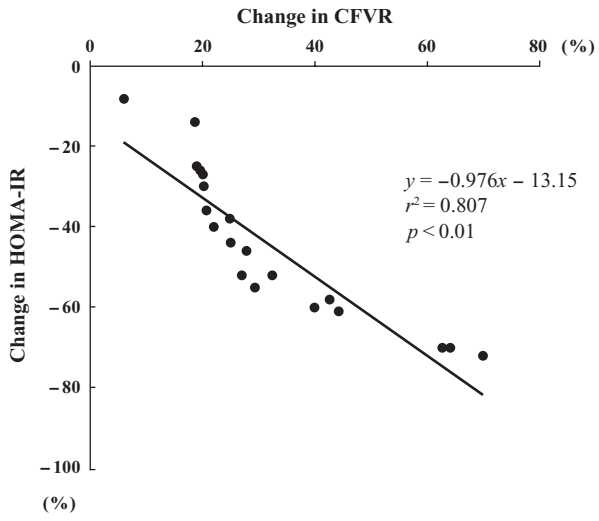

Fig. 4. *Relationship between changes in HOMA-IR and coronary flow reserve ratio (CFVR) in the telmisartan group.*

ACE inhibitor lisinopril but not the ARB losartan. They suggested a possible mechanism is the mediation of endogenous bradykinin potentiation, which improves coronary vasodilatory capacity and increases myocardial capillary density.

In the present study, all the patients were newly diagnosed with hypertension and without LVH (Table 1). Thus, the structural changes in the left ventricle may not have significantly contributed to the improvement in coronary microcirculation. We speculated that restoration of endothelial dysfunction by an ARB may partly induce the improvement in coronary microcirculation.

It is known that the blood-flow response to adenosine is caused primarily through an interaction with the A2-adenosine receptor on vascular smooth muscle cells and has been classically considered endothelium-independent. However, it has been reported that adenosine also acts, at least partially, as an endothelium-dependent vasodilator, *via* both flow-mediated dilatation (*13*) and direct stimulation of endothelial cells (*14*).

Recently, in a randomized, double-blind study measuring forearm blood flow, ARBs were found to reverse endothelial dysfunction by improving NO availability, leading to a reduction in blood pressure; hydrocholorothiazide failed to increase NO availability (*15*). Others have reported that short-term treatment with an ARB (losartan) reversed endothelial-dependent vasomotor dysfunction, as measured by femoral artery flow velocity using a Doppler flow wire, among patients with coronary artery disease, and that long-term therapy with losartan increased NO generation (*16*). Kanemitsu *et al*. (*17*) also reported that administration of an ARB (olmesartan) increased NO level and ameliorated the endothelial dysfunction in *N*-nitro-L-arginine-methyl ester (L-NAME)–treated rats. Morimoto *et al*. (*18*) reported that antihypertensive therapy with telmisartan significantly improved flow-mediated dilatation, a parameter of vascular endothelial function, and brachial-ankle pulse wave velocity, a parameter of arteriosclerosis, as compared with the calcium antagonist amlodipine in patients with essential hypertension, while the antihypertensive effect was not significantly different between the two groups. Several reports examining changes in pulse wave velocity have demonstrated a beneficial effect in improving arterial stiffness independent of reduced BP among patients with hypertension (*19–21*).

We presume that one of the possible mechanisms may include the effect of angiotensin type II receptor–mediated vasodilatation of coronary microarteries, Batenburg *et al*. (*22*) previously showed receptor-mediated vasodilatation in human coronary microarteries in an endothelium-dependent manner, mediated by bradykinin type 2 receptors and NO.

Insulin Resistance and Coronary Circulation

In a cross-sectional study using positron emission tomography, abnormalities in coronary circulatory function were reported to parallel the severity of insulin resistance and carbohydrate intolerance in the progression to type 2 diabetes mellitus with hypertension (*23*). Yokoyama *et al*. (*24*) demonstrated that control of the blood glucose concentration is related to reduced CFR in non–insulin-dependent diabetes mellitus.

ARBs are widely used in the treatment of hypertension and have been shown to restore impaired intracellular insulin signaling and to reduce the incidence of type 2 diabetes, as well as inhibiting the RAS system to decrease blood pressure; ARBs may improve glucose metabolism (*25*). Yamaguchi *et al*. (*26*) also reported that olmesartan increased cyclic adenosine monophosphate (cAMP) and reduced tumor necrosis factor (TNF)-α simultaneously in skeletal muscle of fructose-rich chow rats. They suggested that these results may affect the recovery of insulin resistance. It has also been reported that telmisartan has a unique property in patients with insulin resistance by activating peroxisome proliferator–activator receptor-γ target genes, which are involved in carbohydrate metabolism, and reduced glucose and insulin levels in rats fed a high-carbohydrate diet (*27*).

In the present study, the decrease in HOMA-IR was significantly related to the increase in CFVR in the telmisartan group. Together, these findings support the possibility that telmisartan improves coronary microcirculation partly by ameliorating insulin resistance among essential hypertensive patients without LVH.

Other Possible Mechanisms

It has also been reported that ARBs have unique effects on insulin resistance and circulating levels of adiponectin and highly sensitive C-reactive protein in hypertensive patients with type 2 diabetes (*28*). Others have reported that ARBs effect inflammatory markers, vascular cell adhesion, and

superoxide radicals among patients with stable coronary artery disease (*29*) and hypertension (*30*).) Kadowaki *et al*. (*31*) reported that olmesartan effectively lowered the extent of oxidation of albumin both *in vitro* and *in vivo* in hypertensive hemodialysis patients. In the present study, we did not investigate these markers and have no data about them.

Further studies are required to determine the mechanisms underlying ARBs' beneficial effects on coronary circulation and atherosclerosis.

In conclusion, the results of the present study demonstrate that the inhibition of RAS by the ARB telmisartan, but not with the CCB nifedipine, improved CVFR and insulin resistance in patients with newly diagnosed mild to moderate essential hypertension without LVH.

Study Limitations

Three limitations of this study should be recognized. First, the sample size was not large. Thus, further studies with larger populations are needed. Second, none of the hypertensive patients in this study underwent coronary angiography, because of the lack of clinically suspected coronary artery disease and negative findings of exercise–stress electrocardiography, so we lacked rigorous information about coronary arteries among the present subjects.

Finally, we measured coronary microcirculation and insulin resistance only twice, and the dose of the drug was fixed, so there was no information about the time course and dose-dependency of the drug effect, including the acute effect of ARB.

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