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Angiotensin II Receptor Blocker Prevents Increased Arterial Stiffness in Patients With Essential Hypertension

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Background High pulse wave velocity (PWV) is related to cardiovascular risk in essential hypertension (EHT). It is reported that short-term treatment with an angiotensin II receptor blocker (ARB) decreases PWV, as well as blood pressure (BP), and increases the serum adiponectin, known as an adipocytokine, which has an anti-atherosclerotic effect. However, it is not known whether long-term treatment with ARB prevents the increase in PWV independently of the reduction of BP, and whether adiponectin is related to the chronic effect of ARB on PWV.
Methods and Results In order to examine the short-term effect of ARB on PWV, 9 subjects with EHT had PWV measured before and after treatment with an ARB for 1 month. The treatment significantly reduced PWV and BP. For evaluation of the long-term effect of ARB therapy, 56 consecutive subjects with EHT who were already taking anti-hypertensive drugs other than an angiotensin-converting enzyme inhibitor had their PWV measured. We divided the EHT subjects into 2 groups: (1) the ARB group (EHT treated with an ARB for at least 6 months) and (2) the control group (EHT treated with anti-hypertensive drugs other than an ARB). Although there was no significant difference between the 2 groups in BP, age or body mass index, the PWV value in the ARB group was significantly lower than that in the control group. Moreover, the serum adiponectin concentration in the ARB group was significantly higher than that in the control group.
Conclusions Long-term treatment with ARB inhibits the progression of arterial stiffness independent of BP reduction. One of the mechanisms may be related to the increased serum adiponectin concentration after treatment with an ARB. (*Circ J* 2004; **68:** 1194–1198)

Key Words: Adiponectin; Angiotensin II receptor blocker; Hypertension; Pulse wave velocity

Pulse wave velocity (PWV) reflects arterial distensibility, and aortic PWV in particular is associated with major cardiovascular risk factors and is a strong predictor of prognosis in patients with hypertension[1,2] Aortic PWV, measured from the carotid to femoral arteries, evaluates aortic stiffness, but its measurement requires complex techniques and has not shown reproducibility. Recently, a simple, noninvasive and automatic method of measuring brachial–ankle PWV (baPWV) has been developed, and the validity and reproducibility of this new technique have been demonstrated[3] As it has been reported that the baPWV value has positive correlations with PWV, measured by the classical method, carotid intima–media thickness (IMT) and abdominal aortic calcification[4–6] this new method might enable prediction of the risk of atherosclerosis. Currently, angiotensin II receptor blockers (ARB) are widely used for the treatment of HT because they have been reported to reduce both arterial stiffness and blood pressure (BP)[7] However, BP is one of the main factors affecting arterial stiffness, and the direct effect of ARB on arterial stiffness excluding the effect of BP has not been elucidated

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Adiponectin, an adipocyte-derived protein referred to as Acrp30, apM1, AdipoQ or GBP28, has been identified and characterized[8–12] and in contrast to other adipocyte-derived proteins such as tumor necrosis factor α (TNF-α), plasminogen activator inhibitor-1, leptin and resistin, the circulating concentrations of adiponectin are reduced in patients with coronary artery disease and in states of insulin resistance such as obesity and type 2 diabetes[13–15] It has been suggested that adiponectin enhances insulin sensitivity and prevents atherosclerosis[16,17] We recently reported that treatment with an ARB for a period of 2 weeks not only improved insulin resistance but also increased adiponectin concentrations in subjects with essential hypertension (EHT)[18] The present study was design to test our hypotheses that this improvement of insulin resistance and increase in adiponectin after treatment with an ARB may prevent progression of atherosclerosis or arterial stiffness. One of the aims was to elucidate the long-term effect of ARB on arterial stiffness excluding it effect on BP, and the other was to evaluate the role of adiponectin in the chronic effect of ARB.

Methods

Study Protocol 1

Nine subjects with EHT who had not been taking anti-hypertensive drugs or who had been taking anti-hypertensive drugs other than ARB or angiotensin-converting enzyme inhibitor (ACEI) but whose BP remained high were enrolled. After measurement of baPWV and BP as described later, the subjects were treated with an ARB (80 mg valsartan,

Table 1 Characteristics of the Control and Treatment Groups in Protocol 2

	Control group	*ARB group*	
n	*23*	*33*	
M/F	*10/13*	*19/14*	*NS*
Age (years)	*62.5±1.9*	*59.2±2.0*	*NS*
Body mass index (kg/m²)	*24.1±0.6*	*25.0±0.6*	*NS*
Medications	*1.3±0.1*	*1.6±0.1*	
Calcium channel blocker (%)	*95.6 (22/23)*	*36.4 (12/33)*	
β receptor blocker (%)	*34.8 (8/23)*	*0.6 (2/33)*	
α receptor blocker (%)	*0*	*0.6 (2/33)*	
Diuretics (%)	*0*	*0.6 (2/33)*	
Angiotensin II receptor blocker (%)	*0*	*100 (33/33)*	
		(V: 37%, C: 42%, L: 21%)	

Data are means±SEM.
ARB, angiotensin II receptor blocker; V, valsartan; C, candesartan; L, losartan.

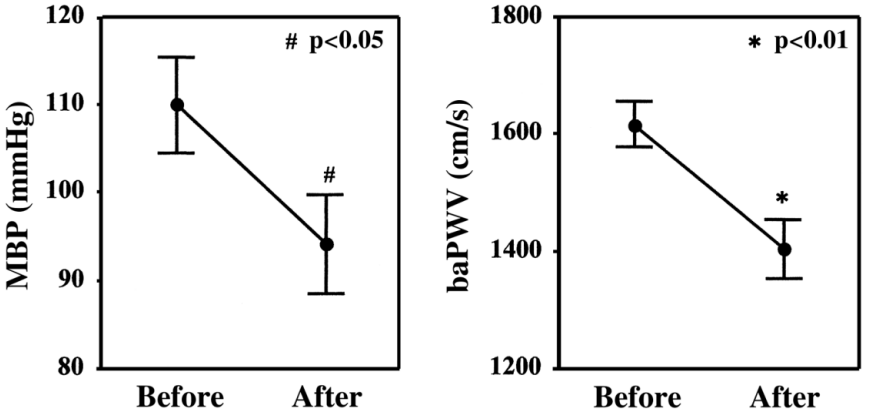

Fig 1. Mean blood pressure (MBP) and brachial–ankle pulse wave velocity (baPWV) before and after treatment with 80 mg/day of valsartan for 1 month. #p<0.05 vs before treatment, *p<0.01 vs before treatment.

PO) for 1 month, after which baPWV and BP were measured again and compared with the baseline values.

Study Protocol 2

One hundred thirty-eight consecutive subjects with EHT who visited Tonan Hospital during the period from May 2002 to April 2003 and agreed to undergo PWV measurement were enrolled and 56 fulfilled the following criteria: (1) medication with anti-hypertensive drugs other than ACEI for at least 6 months, (2) no evidence of diabetes mellitus, and (3) no treatment for hyperlipidemia. The subjects were divided into 2 groups: one group of subjects had already been treated with an ARB (80 mg/day valsartan or 50 mg/day losartan or 8 mg/day candesartan) for at least 6 months (ARB group) and one group of subjects had received anti-hypertensive drugs other than an ARB (control group). Measurement of baPWV and BP was performed as described later, and the values in the 2 groups were compared.

In order to evaluate the detailed mechanisms of the effect on PWV after ARB therapy, we obtained blood samples from the last 26 consecutive patients (13 samples from each group) of the 56 subjects recruited. We measured total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), fasting insulin (F-IRI), serum adiponectin concentration and high-sensitive C-reactive protein (hsCRP) as described later. HOMA (homeostasis model assessment) was calculated as a parameter of insulin sensitivity by the following formula: FPG×F-IRI/405. The values in the ARB group and control group were compared.

Prior to participation, all subjects gave their informed consent and ethical approval.

Measurement of baPWV and BP

baPWV and BP were measured using an automatic waveform analyzer (VaSera VS-1000; Fukuda-Denshi Co, Tokyo, Japan), which calculates PWV based on the time delay between synchronously recorded waveforms of the right brachial artery and each side of the tibial artery. Briefly, occlusion and monitoring cuffs were fitted snugly around both sides of the brachial and ankle regions of each patient while supine. After an appropriate resting interval (10–15 min), the pressure waveforms of all regions were synchronously recorded using the automatic device. The BP of each region was also obtained by the oscillometric method. The baPWV was calculated according to the algorithm of the device. The path lengths from the heart to the right brachial cuff and from the heart to the ankle cuff were measured from the body length, and then the difference between the path lengths was divided by the time interval between the brachial and tibial artery waveforms. The average baPWV of both sides and the average BP of both brachial arteries were used as parameters.

Laboratory Investigations

Blood samples were obtained in the fasting state. The serum adiponectin concentration was measured using a commercially available sandwich enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals Co, Ltd) as previously reported[12] FPG was determined by the glucose oxidase method, F-IRI was measured by radioimmunoassay (Insulin RIA beads, Dianabot) and the serum lipid profile, comprising TC, TG and HDL-C, was estimated by an enzymatic method.

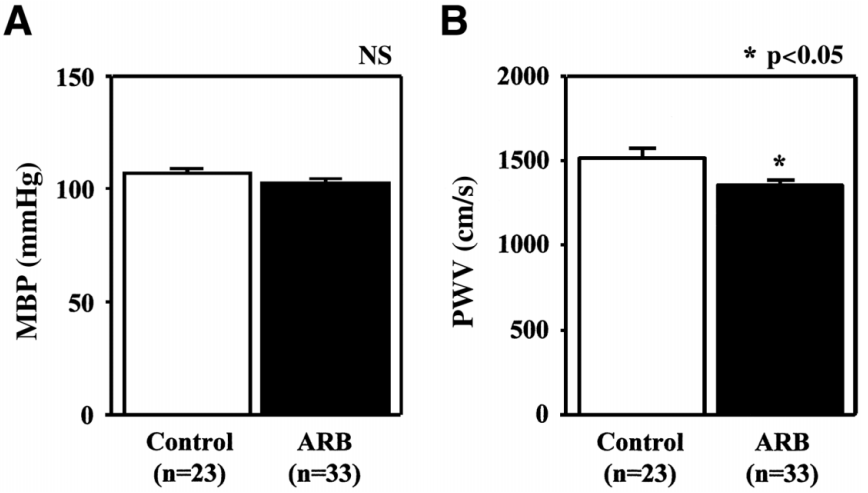

Fig 2. Comparisons of mean blood pressure (MBP) and brachial–ankle pulse wave velocity (baPWV) between the control group and the angiotensin II receptor blocker (ARB) group. Control group: essential hypertension (EHT) treated with anti-hypertensive drugs other than an ARB for at least 6 months; ARB group: EHT treated with an ARB for at least 6 months. *p<0.05 vs control.

Table 2 Characteristics of 26 Subjects With Essential Hypertension

	Control group	*ARB group*	
n	*13*	*13*	
M/F	*9/4*	*7/6*	*NS*
Age (years)	*63.4±2.5*	*58.0±3.7*	*NS*
Body mass index (kg/m²)	*24.0±0.9*	*25.8±0.8*	*NS*
Lipid profile			
Total cholesterol (mg/dl)	*196.3±9.2*	*196.9±6.4*	*NS*
Triglycerides (mg/dl)	*99.1±12.6*	*116.8±16.9*	*NS*
HDL cholesterol (mg/dl)	*50.9±3.4*	*54.3±2.9*	*NS*
Glucose profile			
Fasting plasma glucose (mg/dl)	*101.6±3.6*	*100.8±2.6*	*NS*
Immunoreactive insulin (mU/L)	*6.9±2.0*	*6.3±0.7*	*NS*
HOMA	*1.85±0.58*	*1.56±0.19*	*NS*
BP and PWV			
MBP (mmHg)	*106.4±4.4*	*102.4±3.5*	*NS*
baPWV (cm/s)	*1,544.2±74.4*	*1,352.1±50.7*	*p<0.05*

Data are means ± SEM.
HOMA, homeostasis model assessment; MBP, mean blood pressure; baPWV, brachi-alankle pulse wave velocity; HDL, high-density lipoprotein; ARB, angiotensin II receptor blocker.

Statistical Analysis

All data are expressed as means ± SEM. Group statistical comparisons were assessed by unpaired or paired Student's t-test and the χ^2 test. Differences at $p<0.05$ were considered significant.

Results

Short-Term Effect of ARB on PWV

The basal characteristics of the subjects in this study are shown in Table 1: mean age: 54.7±3.8 years; male/female ratio: 5/4; mean BMI: 24.5±0.9 kg/m². ARB treatment reduced baPWV (from 1605.4±42.6 to 1383.2±51.0 cm/s, $p<0.01$) as well as mean BP (from 107.9±5.7 to 89.9±4.3 mmHg, $p<0.05$) (Fig 1).

Long-Term Effects of ARB on PWV and Adiponectin Concentration

There were no significant differences in gender, age or BMI between the 2 groups. However, the patients in control group were treated with calcium channel blockade and/or β receptor blocker, whereas the patients in ARB group were treated with ARB, calcium channel blocker, β receptor blocker, α receptor blocker, and/or diuretics. In the ARB group, 37%, 42% and 21% of the subjects received valsartan, candesartan and losartan, respectively. Although mean blood pressures (MBPs) were almost the same in the 2 groups (106.2±2.6 vs 101.9±2.1 mmHg) (Fig 2A), baPWV in the ARB group (1356.4±29.2 cm/s) was significantly ($p<0.05$) lower than that in the control group (1517.9±55.8 cm/s) (Fig 2B).

Serum adiponectin concentration and hsCRP were determined from 26 blood samples (13 samples from each group). Although there was no significant difference between control group and the ARB group in MBP, age, gender, BMI, lipid and glucose profiles including HOMA, the baPWV in the ARB group was significantly lower than that in the control group (Table 2). Although there was no significant difference in hsCRP between the control and ARB groups (0.09±0.03 vs 0.09±0.02 mg/dl), the serum adiponectin concentration in the ARB group (8.9±1.0 μg/dl) was significantly ($p<0.05$) higher than that in the control group (6.1±0.8 μg/dl) (Fig 3).

Discussion

We obtained 3 notable findings from the present study. First, treatment with ARB for 1 month reduced baPWV in accordance with a reduction in BP in EHT. Second, long-term treatment (≥6 months) with an ARB prevented an

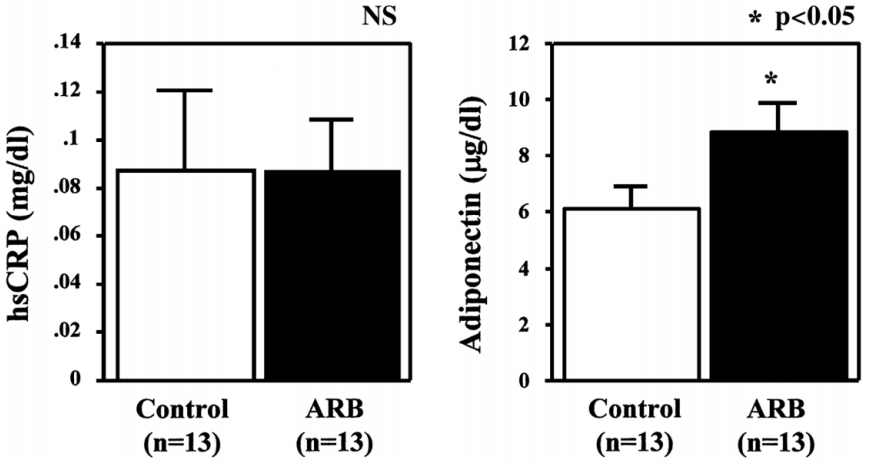

Fig 3. Comparisons of high sensitive C-reactive protein (hsCRP) and serum adiponectin concentration (Adiponectin) between the control group and angiotensin II receptor blocker (ARB) group. Control group: essential hypertension (EHT) treated with anti-hypertensive drugs other than an ARB for at least 6 months; ARB group: EHT treated with an ARB for at least 6 months. *p<0.05 vs control.

increase in baPWV independent of the effect on BP reduction. Third, high adiponectin concentrations were observed in EHT subjects who received long-term treatment with an ARB compared with those not treated with an ARB. These results suggest that long-term treatment of EHT with an ARB prevents increased arterial stiffness by increasing the serum adiponectin concentration independent of the BP reduction effect.

Much interest has been shown over the past few decades in the measurement of PWV as a noninvasive method of assessing atherosclerotic disease. PWV is thought to be a useful method for assessing early-stage atherosclerosis because atherosclerosis is reported to start in the aorta and extend to the cerebral and coronary arteries[1] It has been reported that both the frequency of calcification of the aorta, as seen on computed tomography images, and the carotid IMT, as measured on ultrasonography images, increase as PWV increases[6] Shirakawa et al examined the relationship between PWV and coronary and cerebral arteries in autopsy cases and reported that the more advanced atherosclerosis was, the higher was the PWV value![19] It has been shown that the PWV value in subjects with atherosclerotic diseases, such as HT and diabetes, is higher than in normal subjects[2,20] However, classical methods of measuring carotid–femoral PWV require complex techniques and have not shown reproducibility. VaSera VS-1000, a recently developed device, as well as Form ankle-brachial pressure index (ABI)/PWV enables simultaneous measurements of the BP of the limbs and can calculate ABI and baPWV in a short time. Moreover, reproducible results can be obtained regardless of the operator's technique (intra-observer reproducibility is 10%)[3] However, this method differs from that used for carotid-femoral PWV, and the baPWV values cannot be simply compared with the PWV values obtained by the classical methods, although baPWV has a significant positive correlation with the classical PWV and with carotid IMT[4] Therefore, this method might enable prediction of the risk of atherosclerosis and high values may mean that the atherosclerotic process is already well established.

Mahmud et al reported that treatment with valsartan for 4 weeks significantly reduced PWV in accordance with BP reduction[7] An acute functional change in vascular smooth muscle relaxation, improvement in endothelial dysfunction, decrease in arterial wall thickness, decrease in collagen content and reversal of smooth muscle cell hypertrophy have been proposed as mechanisms of the improvement in PWV by ARB[21–23] However, it is unlikely that treatment with ARB for only 4 weeks would improve the structure of the vasculature. Short-term treatment of ARB may improve PWV mainly through functional mechanisms such as vascular smooth muscle relaxation and improvement in endothelial dysfunction, because BP was also decreased after ARB treatment. The main objectives of anti-hypertensive therapy are prevention of atherosclerosis and reduction of the incidence of cardiovascular events, which is why it is important to evaluate the long-term effect of ARB on PWV. As shown in Fig 2, although the BP in the control group and the ARB group were almost the same, the PWV value in the control group was significantly higher than that in the ARB group. These results suggest that ARB treatment may result not only in functional improvement of the vasculature but also in structural improvements, such as decreased arterial wall thickness, decreased collagen content and reversal of smooth muscle cell hypertrophy.

Adiponectin is a recently discovered adipocytokine produced from adipocytes[8–12] and it is suggested that this protein enhances insulin sensitivity and prevents atherosclerosis[16,17] We have already reported that short-term treatment with an ACEI (temocapril) or ARB (candesartan) increased the circulating adiponectin concentration as well as improving insulin sensitivity[18] However, it is difficult to discuss the effect of ARB on atherosclerosis or arterial stiffness from this findings of study 1 because the subjects were treated for only 2 weeks. We therefore designed study 2 to evaluate the long-term effect of ARB on the serum adiponectin concentration. Interestingly, although there were no significant differences in age, gender, BMI, lipid and glucose profiles and BP between patients who received and those who did not receive ARB treatment, the serum adiponectin concentration was significantly higher in patients who received long-term ARB therapy. These results indicate that ARB may reduce arterial stiffness by increasing the serum adiponectin concentration independent of the effect on BP. The mechanisms of this effect are unclear, but speculations can be made on the basis of results of previous study. One possibility is that ARB causes an increase in adipogenesis that results in a greater net capacity for adiponectin production, because it has been found in an in vitro study that angiotensin II markedly inhibits adipogenic differentiation of human adipocytes via the angiotensin type I receptor[24] Moreover, because it has been shown that TNF-α suppresses the expression and secretion of adiponectin in 3T3-L1 adipocytes and that ARB decreases

TNF-α concentration in skeletal muscle and mononuclear cells, but not yet confirmed in adipose tissue, the increase in adiponectin secretion could be caused by a decrease in TNF-α concentrations or actions in adipocytes.[25,26]

It is well established that vascular inflammation and insulin resistance are independent risk factors for the development of atherosclerosis, and it is well known that angiotensin II causes vascular inflammation and reduces insulin sensitivity.[18,27–29] However, there was no significant differences between the groups treated by anti-hypertensive drugs with or without ARB in hsCRP and HOMA which are the parameters of inflammation and insulin sensitivity. These data indicate that the effect of ARB on arterial stiffness is strongly related to an increase in serum adiponectin concentration rather than to an anti-inflammatory effect or an improvement in insulin resistance. However, the effect of ARB on insulin sensitivity may be masked, because 95% of the patients in the control group were being medicated with a calcium channel blocker, which has also been reported to improve insulin sensitivity,[30] and also HOMA is not as valuable for the evaluation of insulin sensitivity as the glucose clamp method.

Study Limitations

This was a retrospective and a cross-sectional study, not a prospective study, so it is difficult to know whether adiponectin directly effects PWV after treatment with an ARB. Moreover, even though there were no significant difference in clinical background between the groups, we can not exclude the effect of other factors influencing the PWV value or the serum adiponectin concentration, because the groups of subjects were not randomized. In order to clarify these issues, further prospective and randomized studies will be needed.

In conclusion, long-term blockade of the renin-angiotensin system may be suitable treatment for preventing increased arterial stiffness and may reduce the incidence of cardiovascular events. The reduction of arterial stiffness after long-term treatment of ARB may be related not only to the effect of BP reduction but also to an increase in the serum adiponectin concentration.

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