Original Article

Reduction of QTc Dispersion by the Angiotensin II Receptor Blocker Valsartan May Be Related to Its Anti-Oxidative Stress Effect in Patients with Essential Hypertension

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QT dispersion has been reported to increase in patients with essential hypertension, and abnormal QT dispersion is associated with arrythmias and sudden cardiac death. However, whether change in QT dispersion is related to oxidative stress is unclear. We examined the effect of the angiotensin II receptor blocker valsartan on QT dispersion and the relationship between oxidative stress and QT dispersion in patients with essential hypertension. Hypertensive patients whose systolic blood pressure (SBP) was more than 140 mmHg and/or diastolic blood pressure (DBP) was more than 90 mmHg were treated with valsartan. Blood pressure was measured once a month for 6 months. The difference between the maximal and minimal QT intervals within a 12-lead surface ECG was measured and QT dispersion and QTc dispersion corrected by heart rate were obtained before and 6 months after treatment. Left ventricular mass (LVM) assessed by echocardiography was obtained at baseline and 6 months after treatment. Venous blood samples were obtained at baseline and 6 months after treatment to measure serum levels of lipoperoxidation (LPO) and type I and III procollagen. Treatment with valsartan significantly decreased SBP and DBP. QTc dispersion decreased significantly 6 months after treatment with valsartan as compared to the baseline values. Valsartan treatment did not affect the LVM. Valsartan significantly decreased the abnormally high LPO levels. The changes in QTc dispersion were positively correlated with changes in the serum levels of LPO and with changes in DBP. The correlation between changes in LPO and QTc dispersion was more close than that between changes in DBP and QTc dispersion. In conclusion, antihypertensive therapy with valsartan reduces QTc dispersion and this may be related to the ability of valsartan to reduce oxidative stress in patients with essential hypertension. (*Hypertens Res* 2007; 30: 307–313)

***Key Words*: valsartan, blood pressure, QT dispersion, oxidative stress**

Introduction

Hypertension is one of the risk factors for cardiovascular disease (*1*, *2*). In addition, hypertension causes cardiac hypertrophy and fibrosis (*3*, *4*). QT dispersion is the difference between the maximal and minimal QT intervals within a 12-lead surface ECG (*5*), and is regarded as representing the degree of repolarization inhomogeneity in the heart (*6*). Abnormal QT dispersion is associated with arrythmias and cardiac sudden death (*7–9*). QT dispersion has been reported to increase in left ventricular (LV) hypertrophy (*10*) and

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Table 1. Patients Characteristics

Age (years old)	71.9±2.5
Gender (male/female)	9/8
Diabetes melitus (*n* (%))	2 (11.8)
Hyperlipidemia (*n* (%))	10 (58.8)
History of hypertension (years)	5.5±1.2

Table 2. Changes in Parameters

	Before treatment ($n=17$)	6 months after treatment ($n=17$)	p value
Body weight (kg)	59.2±12.4	59.0±12.6	n.s.
BMI (kg/m^2)	24.2±3.9	24.1±3.9	n.s.
SBP (mmHg)	155.1±11.6	134.0±10.9	<0.01
DBP (mmHg)	86.4±12.6	71.8±12.9	<0.01
HR (beats/min)	74.1±12.4	74.8±8.1	n.s.
Creatinine (mg/dl)	0.8±0.2	0.7±0.1	n.s.
BUN (mg/dl)	14.3±3.4	15.6±4.1	n.s.
AST	23.4±7.3	23.9±7.0	n.s.
ALT	19.0±7.4	18.9±6.0	n.s.
γ-GTP	27.9±14.7	28.1±10.5	n.s.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; n.s., not significant.

hypertension (*11*, *12*). Since angiotensin II has been implicated in the hypertrophy of myocytes (*13*) and modification of the cellular matrix (*14*), it is hypothesized that an angiotensin II receptor blocker would reduce QT dispersion. Furthermore, it has been reported that the oxidative stress in patients with myocardial infarction is related to a decrease in exercise-induced QT dispersion (*15*). However, it is unclear whether changes in QT dispersion are related to oxidative stress in patients with hypertension. Therefore, the aim of the present study was to examine whether an angiotensin II receptor blocker, valsartan, would reduce QT dispersion and whether changes in QT dispersion are related to the oxidative stress in patients with essential hypertension.

Methods

Subjects

We prospectively studied 17 patients with mild-to-moderate hypertension whose systolic blood pressure (SBP) was more than 140 mmHg and/or whose diastolic blood pressure (DBP) was more than 90 mmHg with or without antihypertensive drugs. All patients had been outpatients of Chikaishi Hospital and Gujo Municipal Hospital, both of which are affiliated with Gifu University Hospital, and had been diagnosed with essential hypertension and confirmed not to have secondary hypertension at least 6 months before entry into this study. The characteristics of the patients are listed in Table 1. All the patients were treated with 40 mg or 80 mg of valsartan. We first prescribed 40 mg of valsartan, but if blood pressure did not decrease to less than 140/90 mmHg, 80 mg of valsartan was used. The patients were treated with valsartan alone ($n=7$), valsartan + Ca channel blocker ($n=8$), valsartan + Ca channel blocker + β-blocker ($n=1$), or valsartan + Ca channel blocker + β-blocker + diuretics ($n=1$). In 4 patients, statins were used throughout the study.

The study protocol was approved by the Ethics Committee of Gifu University School of Medicine. Informed consent was obtained from each patient before starting this study.

Follow-Up

All subjects were followed-up by doctors at the outpatient clinic of each hospital and were treated with the aim of reducing SBP and DBP below 140/90 mmHg through standard lifestyle modification and pharmacological intervention. We aimed to maintain blood pressure strictly below 140/90 mmHg throughout the 6-month follow-up period. Blood pressure was measured using a sphygmomanometer once a month at the outpatient office and echocardiography was undertaken before and after 6 months of follow-up. None of the patients experienced any cardiovascular events during the 6-month follow-up period.

Blood Pressure Measurement

Office blood pressure was measured with a standard mercury sphygmomanometer after the subject had been seated for at least 10 min. Three consecutive measurements were obtained and the mean of the last two was regarded as the blood pressure.

Electrocardiography

Standard 12-lead ECGs were recorded using a paper speed of 25 mm/s at baseline and 6 months after treatment. A single observer blinded to the protocol of the present study analyzed all ECGs. The difference between the maximal and minimal QT intervals within a 12-lead surface ECG was measured, the QT dispersion was obtained, and then the QTc dispersion was obtained by correction of the heart rate (*5*).

Echocardiography

An M-mode echocardiographic study of the left ventricle (LV) was performed under cross-sectional control with a commercially available machine (Prosound II SSD-6500 SV; Aloka, Tokyo, Japan). Echocardiographic examinations were conducted by two expert physicians and tracings were read by two other investigators. At the time of the echocardiographic examination, all investigators were unaware of the patients'

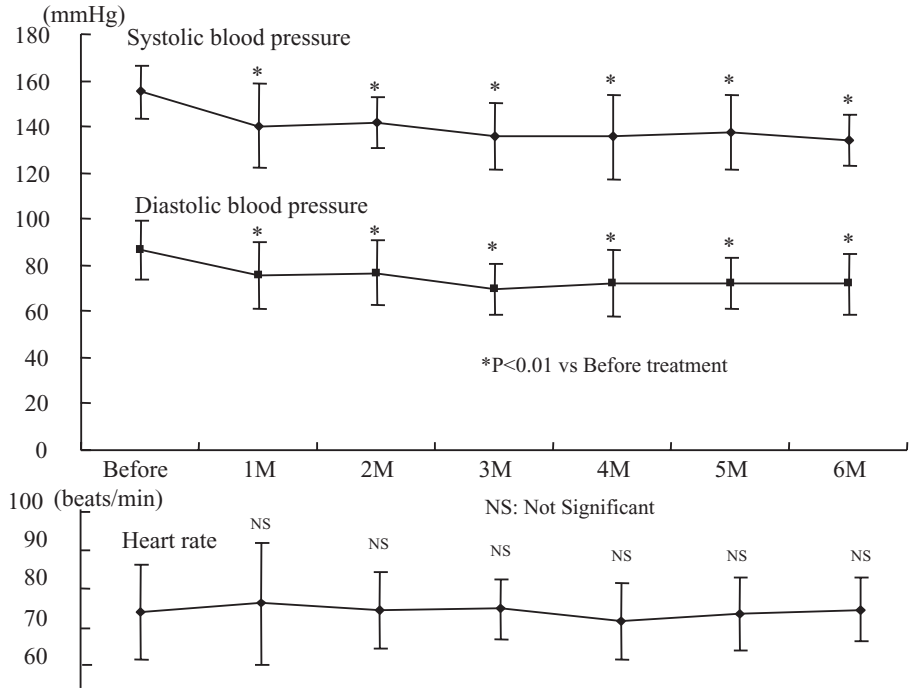

Fig. 1. *Time-course of changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) between before and during the treatment with valsartan.*

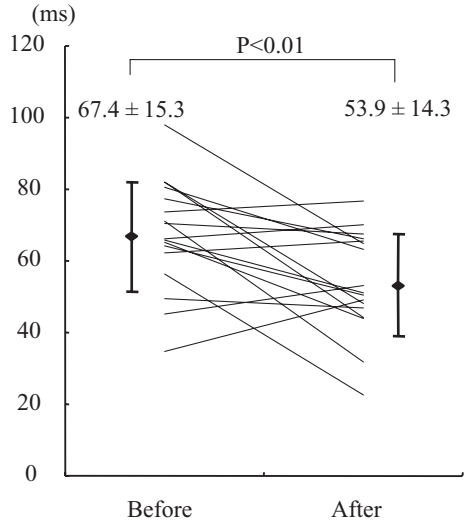

Fig. 2. *Changes in QTc dispersion between before and after 6 months of treatment with valsartan.*

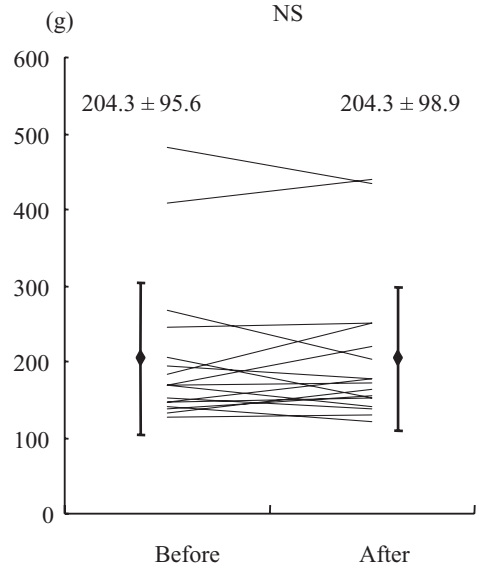

Fig. 3. *Left ventricular mass (LVM) at the baseline visit and at the end of the 6-month follow-up period.*

clinical data, including office blood pressure, medications and cardiovascular complications. LV mass (LVM) was determined according to the formula introduced by Devereux *et al*. (*16*):

$$LVM = 1.04\ \{(IVSTd + LVDd + PWTd)^3 - LVDd^3\} - 13.6\ (g),$$

Where IVSTd, diastolic interventricular septum; LVDd, LV diastolic diameter; PWTd, diastolic posterior wall thickness. We used an absolute value of LVM but not LVM index

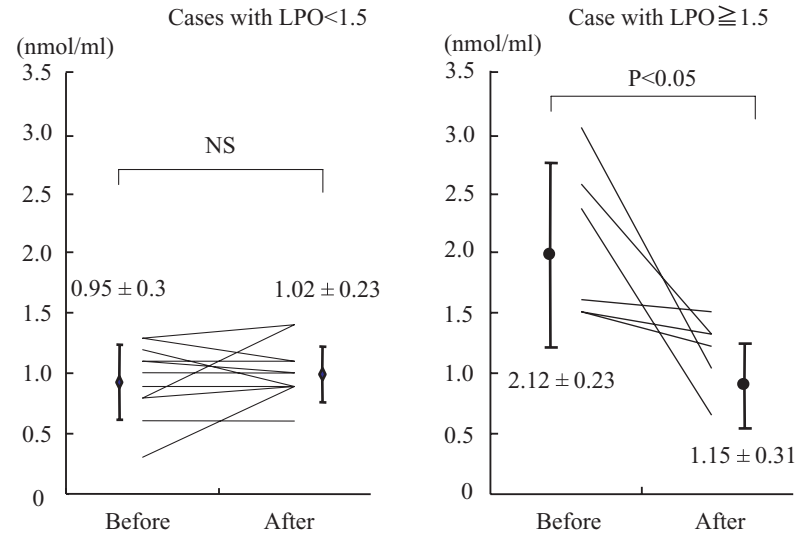

Fig. 4. *Changes in the serum levels of lipoperoxidation (LPO).*

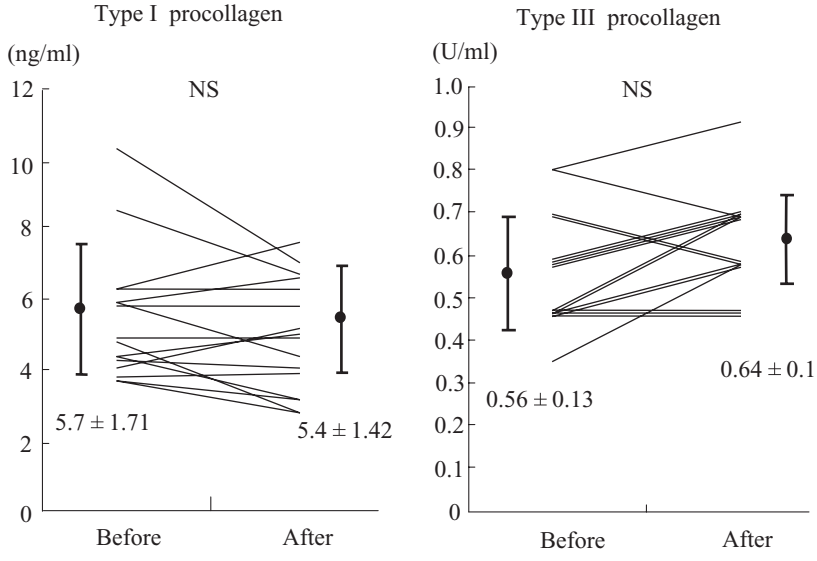

Fig. 5. *Changes in the serum levels of type I and type III procollagen.*

(LVMI) corrected by body surface area to investigate the change of LV hypertrophy based on the report by Dahlof *et al*. (*17*). This is because body weight change substantially affects body surface area and results in a change of LVMI, and therefore we considered that the absolute LVM is a good indicator of LV hypertrophy without any influence of body weight change.

Serum Levels of Lipoperoxidation and Type I and III Procollagen

Venous blood samples were obtained at baseline and 6 months after treatment to measure serum levels of lipoperoxidation (LPO) and type I and III procollagen. Serum LPO was used as an indicator of oxidative stress (*18*), and serum type I and III procollagen were used as indicators of fibrosis (*19*, *20*).

Statistical Analysis

All values are expressed as the mean±SD. Differences were assessed by the paired Student's *t*-test and p values <0.05 were considered to indicate statistical significance.

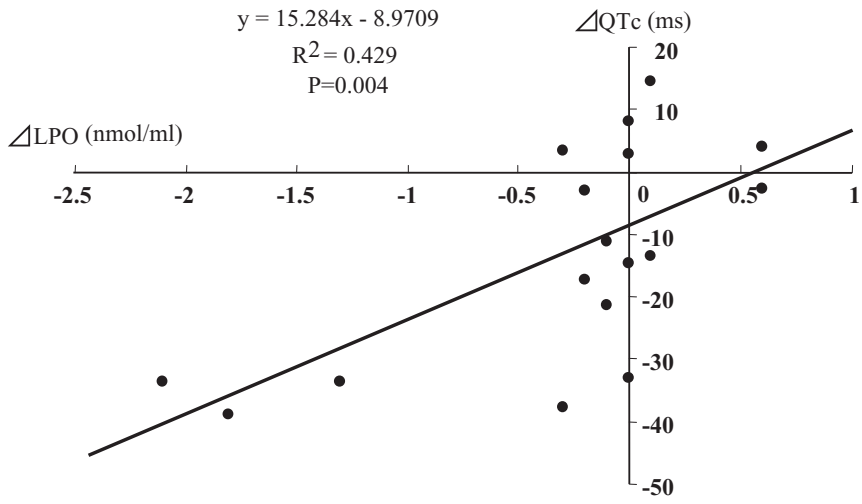

Fig. 6. *Relationship between the changes in the serum levels of LPO and the changes in QTc dispersion.*

Results

Patients' Characteristics and Changes in Parameters

Table 1 shows the main characteristics of all patients at baseline. Table 2 shows the patients' parameters. There were no abnormal laboratory findings before or after treatment.

Time Course of Changes in Blood Pressure and Heart Rate

The time-course of changes in SBP and DBP over the 6 months of follow-up is shown in Fig. 1. Treatment with valsartan significantly decreased SBP and DBP. There was no significant change in heart rate between before and during valsartan treatment (Fig. 1).

QTc Dispersion

As shown in Fig. 2, QTc dispersion decreased significantly 6 months after treatment with valsartan.

LVM

Figure 3 shows the LVM before (baseline visit) and after 6 months of follow-up. There were no significant differences in LVM between baseline and the end of the 6-months follow-up.

Serum Levels of LPO and Type I and Type III Procollagen

As shown in Fig. 4, serum levels of LPO, an indicator of oxidative stress, did not differ between baseline and 6 months after treatment with valsartan in cases with serum levels of LPO less than 1.5 pg/ml, the upper limit of the normal range. However, in cases with serum levels of LPO more than 1.5 pg/ml, serum levels of LPO were found to have significantly decreased when the levels at baseline and 6 months after valsartan treatment were compared. As shown in Fig. 5, the serum levels of type I and type III procollagen did not differ between baseline and 6 months after valsartan treatment.

Relationship between Changes in Serum Levels of LPO and QTc Dispersion

As shown in Fig. 6, the changes in the serum levels of LPO were positively correlated with QTc dispersion.

Relationship between Changes in SBP and DBP and QTc Dispersion

As shown in Fig. 7, the changes in QTc dispersion were positively correlated with changes in DBP but not SBP.

Discussion

The present study demonstrated that treatment with valsartan decreased SBP and DBP, and a strict lowering of blood pressure for 6 months significantly decreased QTc dispersion in patients with essential hypertension. The changes in QTc dispersion were positively correlated with the changes in LPO, an indicator of oxyradicals.

QT dispersion is reported to be associated with malignant arrythmias and sudden cardiac death (*7–9*). Therefore, a reduction in QT dispersion may lead to a reduction in the rate of arrythmias and sudden cardiac death. It has been reported that the D-allele of the angiotensin-converting enzyme (ACE)

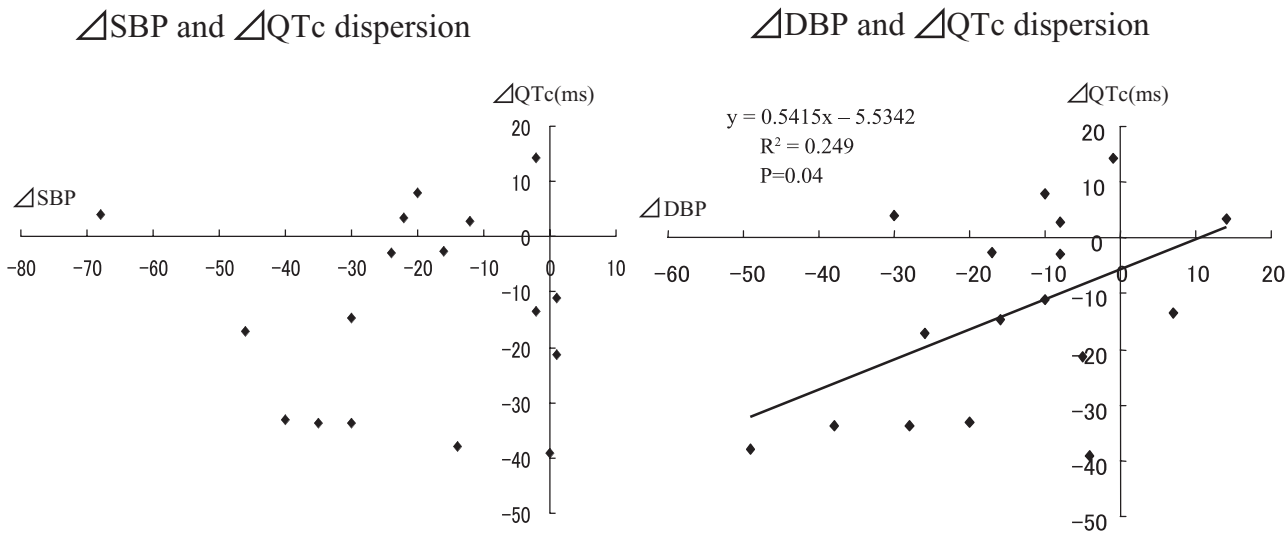

Fig. 7. *Relationship between the changes in systolic blood pressure (SBP) or diastolic blood pressure (DBP) and the changes in QTc dispersion.*

polymorphism is related to increased QT dispersion in patients after myocardial infarction, suggesting that the renin-angiotensin system may be involved in the increased QT dispersion (*21*). This may be supported by the finding that treatment with ACE inhibitors reduced QT dispersion in patients with hypertension and chronic heart failure (*22*, *23*). In the present study, treatment with valsartan significantly decreased QTc dispersion. This is consistent with previous reports demonstrating that an angiotensin II receptor blocker, irbesartan, reduced QT dispersion in patients with hypertension (*24*, *25*). Stimulation of angiotensin II receptors causes LV hypertrophy (*26*) and modifies the cellular matrix (*27*). These changes may cause increased QT dispersion. Also, it has been reported that a reduction in LV hypertrophy leads to a reduction in QT dispersion (*28*). However, in the present study, LVM as assessed by echocardiography was unchanged between before and after the 6 months of treatment with valsartan. The serum levels of type I and type III procollagen also did not differ between baseline and 6 months of treatment. These results suggest that the reduced QT dispersion in the present study was not caused by a reduction in LV hypertrophy or reduction in the fibrosis of the heart. On the other hand, oxidative stress has been reported to be related with hypertension (*29*) and there has also been a report that the antioxidants vitamins C and E decreased exercise-induced QT dispersion after myocardial infarction (*15*). As shown in the present study, although mean serum levels of LPO, an indicator of oxidative stress, did not differ between baseline and 6 months after treatment with valsartan in patients with normal serum LPO levels, abnormally high serum levels of LPO, more than 1.5 pg/ml, the upper limit of the normal range, decreased significantly by 6 months of treatment with valsartan. Furthermore, in the present study, the changes in the serum levels of LPO were positively correlated with the changes in QTc dispersion, suggesting that the reduction in QTc dispersion was caused by the reduction in oxidative stress after the treatment with valsartan.

Study Limitation

This study did not have a control-group arm to examine the effect of the reduction of blood pressure. Therefore, the relationship between the decrease in blood pressure and the change in QTc dispersion was obtained. As a result, there was a roughly positive relationship between the decrease in DBP and the decrease in QTc dispersion, as shown in Fig. 7. However, the coefficient index was larger in the relationship between changes in QTc dispersion and plasma LPO levels than in that between the changes in DBP and QTc dispersion, suggesting that plasma LPO levels are more likely to affect the changes in QTc dispersion.

In conclusion, antihypertensive therapy with the angiotensin II receptor blocker valsartan reduces QT dispersion without affecting LVM. This effect may be caused by a reduction in oxidative stress due to valsartan.

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