

Acute Effects of Angiotensin II Receptor Blocker on Ventricular Repolarization Alternans in Chronic Heart Failure

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Repolarization alternans, which can be detected clinically as microvolt-level T-wave alternans (TWA), is considered an important mechanism underlying the initiation of ventricular tachycardia/ventricular fibrillation (VT/VF) linked to sudden cardiac death (SCD). Recently, the rennin-angiotensin system (RAS) inhibitors have been suggested to have potential benefits in reducing SCD as well as heart failure death with chronic heart failure (CHF).

In this study, we tested the acute effects of an angiotensin II receptor blocker (ARB), valsartan, on the development of TWA and the heart rate at which TWA appeared (onset heart rate; OHR). Fifty consecutive patients with CHF underwent TWA measurement. Patients with positive TWA were administered valsartan (80mg/day) orally for 3 days. Alternans voltage in the vector magnitude lead (Valt) and the OHR were compared before and after the drug exposure.

TWA was positive in 19 patients (38%), negative in 16 (32%), and indeterminate in 15 (30%). Nineteen patients with positive TWA received valsartan. However, 3 patients were withdrawn due to adverse drug reactions. In all the remaining 16 patients, markedly reduced Valt ($6.1 \pm 3.8 \mu\text{V}$ to $2.5 \pm 1.9 \mu\text{V}$; $P = 0.002$) and increased OHR (94 ± 9 beats/min to 102 ± 9 beats/min; $p = 0.002$) were observed. In particular, 3 patients became TWA negative.

These results suggest that the RAS inhibitors prevent SCD by the improvement of repolarization abnormality.

Life-threatening arrhythmias such as ventricular tachycardia/ventricular fibrillation (VT/VF) can often link to the genesis of sudden cardiac death (SCD). Recent theoretical and experimental reports have proposed repolarization alternans (i.e. action potential duration (APD) alternans) as a critical triggering mechanism for the initiation of VT/VF (1, 2). Using spectral method, APD alternans can clinically be detected as T-wave alternans (TWA) at microvolt level, which is a heart rate-dependent beat-to-beat ECG representation of the ventricular repolarization process, and is shown to affect susceptibility to malignant ventricular arrhythmias in various cardiac diseases (3-9). In addition, we previously reported that TWA occurring at a sufficiently low heart rate is associated with increased risk of SCD in nonischemic dilated cardiomyopathy (10). Therefore, this technique is now recognized as a non-invasive tool for identifying patients who will benefit from prophylactic treatment and has the possibility of guiding the use of antiarrhythmic agents.

Recently, a new approach to antiarrhythmic therapy has emerged from the concept of electrical and structural ventricular remodeling leading to the genesis of VT/VF. Remodeling is altered structure/function of ion channels, gap junctions, myocytes, and tissue architecture, which might be deleterious and arrhythmogenic in the long run. Upstream elements in this remodeling are long-term modulators of structure/function that change the expression of molecules contributing to the arrhythmic substrate. Reducing these elements would be expected to prevent ventricular remodeling and, hence, VT/VF. One important target of these upstream elements is believed to be the rennin-angiotensin system (RAS). In fact, angiotensin II (Ang II), which is the main product of the RAS, has evidences of short- and long-term modulations of ion channel and gap junction functions (11-14) in addition to myocardial hypertrophy (15) and fibrosis (16), and so Ang II can be an important modulator of arrhythmic substrate. However, there is no direct evidence of the effect of Ang II on repolarization alternans. Therefore, the present study was performed to clarify the acute effects of Ang II receptor blocker (ARB), on the development of repolarization alternans and the heart rate (onset heart rate ; OHR) at which this occurs in patients with chronic heart failure (CHF) by using TWA measurement.

METHODS

Patient population. We investigated 50 consecutive patients with CHF who were referred to the Kobe University Hospital between June 2001 and May 2004. All patients underwent both noninvasive and invasive evaluation, including TWA determination during ergometer exercise stress testing. All patients were in sinus rhythm and none was treated with beta-blockers, angiotensin converting enzyme inhibitors (ACE-Is), or Vaughan-Williams class I antiarrhythmics before entering this study. If such drugs had been administered before recruitment, they were withdrawn for at least 5 half-lives. Exclusion criteria were as follows: (A) current treatment with Vaughan-Williams class III antiarrhythmics; (B) adverse reactions to ARB; and (C) renal dysfunction with serum creatinine ≥ 2.0 . Non-sustained ventricular tachycardia (NSVT) was defined as present if at least one episode of ≥ 3 consecutive premature beats at a rate of ≥ 100 bpm was documented. Sustained VT (SVT) was defined as a documented episode of tachycardia of ventricular origin at a rate of > 100 bpm and lasting for > 30 seconds, or resulting in hemodynamic collapse. The Ethics Review Board of Kobe University Hospital approved the protocol of this study, and written informed consent was obtained from all participants.

Measurement of TWA. TWA was measured at rest and during controlled bicycle exercise testing using a CH 2000 system (Cambridge Heart, Inc., Bedford, MA) as previously described, by an investigator who was blind to all clinical data. In the present study, to ensure accuracy of measurements, the exercise protocol was constructed as follows. Exercise workload was gradually increased in a stepwise manner to avoid sudden elevation of heart rate and patients were instructed to maintain a pedaling rate of 0.33 or 0.66 cycle/beat to avoid the interferences. TWA was prospectively defined as positive when it was sustained with an alternans voltage of $1.9 \mu\text{V}$ in the vector magnitude lead (Valt) during exercise with an OHR ≤ 110 bpm or below 70% of maximum predicted heart rate, or with an alternans voltage of $1.0 \mu\text{V}$ at rest for a period of at least 1 minute, provided that the alternans ratio was ≥ 3 . TWA was prospectively defined as negative if artifact-free criteria were met while the heart rate was maintained at a level of ≥ 105 bpm. Otherwise, TWA was defined as indeterminate (5, 17). The onset heart rate for TWA was determined while heart rate was stable and constant. To assess intra-individual reproducibility of TWA, 7 randomly selected patients with positive TWA underwent two consecutive TWA

ACUTE EFFECTS OF ARB ON TWA

measurements 30 minutes apart. Patients with positive TWA were administered valsartan (80mg) orally once in the morning for three days, and TWA was measured again 6 hours later after the drug administration on the third day. The following data were obtained before and after drug administration: (A) resting heart rate; (B) presence of TWA; (C) OHR; and (D) left ventricular end-diastolic diameter (LVDd) and left ventricular ejection fraction (LVEF) calculated by M-mode and two-dimensional echocardiography.

Statistical Analysis. Values are expressed as mean \pm SD for continuous variables and as percentages for categorical variables. Patient groups were compared by the unpaired *t* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Paired variables before and after drug administration were compared by paired *t* test. A statistical probability of < 0.05 was considered significant.

RESULTS

Study patients. The study group consisted of 50 consecutive patients with CHF: 42 men and 8 women with a mean age of 64 ± 10 years. Underlying heart disease was ischemic in 19 cases and nonischemic in 31. Mean LVEF was 35 ± 9 % and New York Heart Association (NYHA) functional class was 2.7 ± 0.7 . Clinical characteristics of the participants are listed in Table 1.

Characteristics	N=50
Age (yrs)	64 ± 10
Gender: M/F	42 / 8
NYHA	2.7 ± 0.7
LVEF (%)	35 ± 9
LVDd (mm)	56 ± 10
ICM/Non-ICM (%)	38 / 62

Data are as the mean \pm SD or percentage of patients. NYHA indicates New York Heart Association class; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; ICM, ischemic cardiomyopathy; Non-ICM, nonischemic cardiomyopathy.

Baseline characteristics of TWA measurement. Nineteen patients (38 %) were TWA positive (group A), 16 (32 %) were TWA negative (group B), and 15 (30 %) were TWA indeterminate. Patients with TWA indeterminate results were excluded from the study because of poor electrocardiogram recording with noise ($n=5$), frequent ectopic beats ($n=6$), and failure to achieve a heart rate of 105 beats/min ($n=4$). In group A, alternans voltage in the vector magnitude lead and OHR were 6.1 ± 3.8 μ V and 94 ± 9 beats/min, respectively. In addition, among group A, repeated baseline TWA testing was performed in 7 randomly selected patients whose clinical characteristics were comparable to those of the entire study cohort. TWA amplitude and OHR were comparable between both tests (Valt and OHR; 5.1 ± 1.5 μ V vs. 5.1 ± 1.7 μ V; 97 ± 8 beats/min vs. 96 ± 7 beats/min, respectively). Clinical parameters did not differ significantly between group A and group B, with the exception of previous history of VT and LVDd prior to TWA testing (Table 2); previous history of VT was significantly higher and LVDd was significantly larger in group A compared with in group B, in accordance with our previous report (7).

TABLE 2. Clinical Characteristics in the 2 Groups

Variables	TWA positive	TWA negative	<i>p</i>
Patients (n)	19	16	
Age (yrs)	65 ± 8	63 ± 10	NS
LVEF (%)	34 ± 10	35 ± 8	NS
LVDD (mm)	63 ± 7	54 ± 8	<i>p</i> < 0.05
VT (%)	53	19	<i>p</i> < 0.05
NSVT (n)	7	3	
SVT (n)	3	0	
ICM (%)	37	31	NS
Non-ICM (%)	63	69	NS

Individual variables were compared statistically in the two groups of TWA positive and negative. VT indicates ventricular tachycardia; SVT, sustained ventricular tachycardia; NSVT, non-sustained ventricular tachycardia. Other abbreviations are the same as in Table 1.

Response of TWA to ARB. Nineteen patients with TWA positive results were administered valsartan 80 mg/day for 3 consecutive days. During the drug administration period, 3 patients were withdrawn from the study because of adverse effect including deterioration of renal function, excessive hypotension, and atrial fibrillation. Consequently, the final data analysis comprised 16 patients. Valsartan significantly attenuated alternans power of TWA in all patients ($6.1 \pm 3.8 \mu\text{V}$ to $2.5 \pm 1.9 \mu\text{V}$; $p = 0.002$) (Figure 1). In particular, TWA status changed from positive to negative in 3 patients. A representative example of these patients is shown in Figure 2. Furthermore, OHR of TWA increased significantly from 94 ± 9 to 102 ± 9 beats/min ($p = 0.001$) (Figure 2). In contrast, there were no statistically significant differences in resting heart rate, blood pressure, or echocardiographic variables before and after drug administration (Table 3).

Figure 1. Representative Case at Orthogonal X, V, Z Configuration

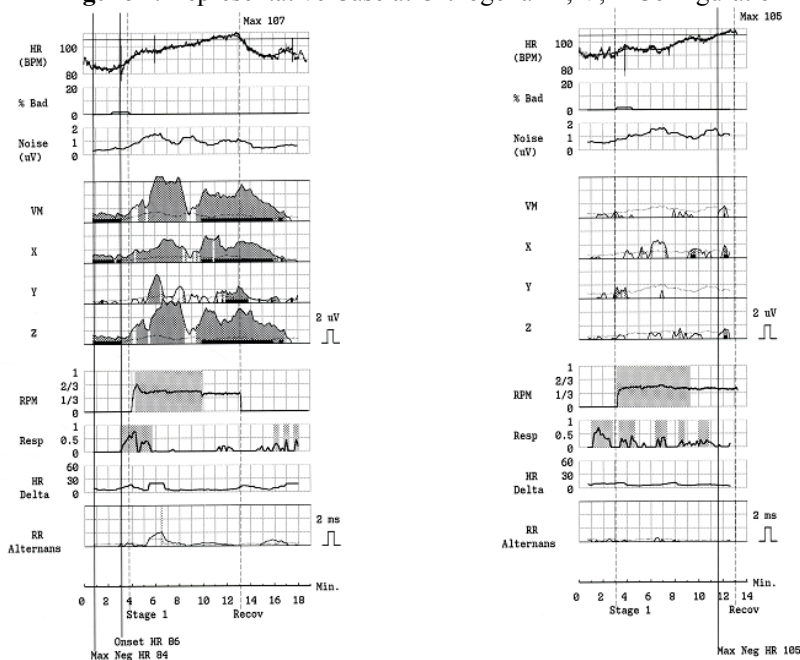


FIG. 1. Representative case of a patient whose TWA status changed from positive to negative during exercise testing following administration of valsartan (left: before drug administration; right: after drug administration).

ACUTE EFFECTS OF ARB ON TWA

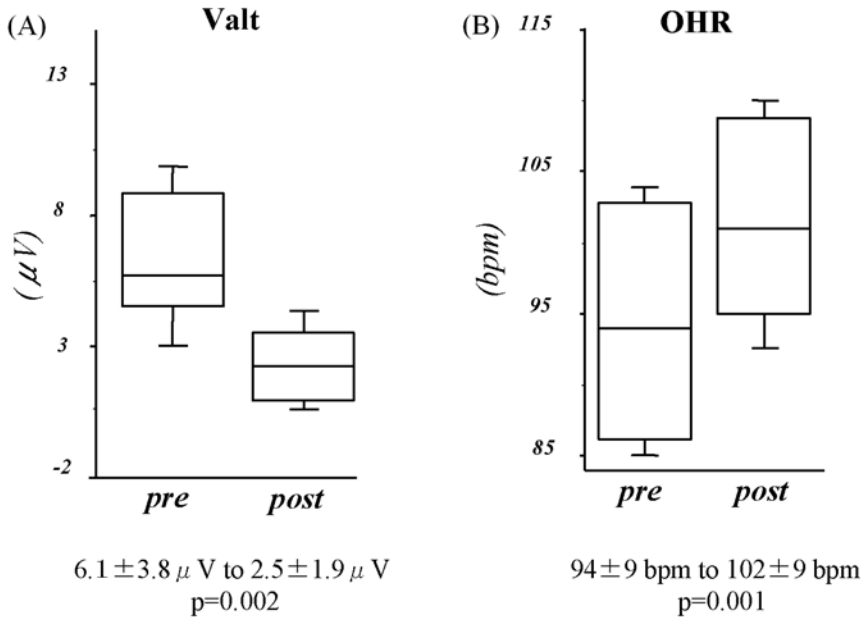


FIG. 2. (A) Changes in TWA amplitude in the vector magnitude lead (Valt) and **(B)** onset heart rate (OHR) following drug administration. Each box plots the range of each value and error bars represent standard error of the mean. Central lines represent distribution median. For the y-axes, μV = microvolts, bpm = beats per minute.

TABLE 3. Effects of ARB on hemodynamics and Cardiac Performances

	Before	After	<i>p</i>
SBP (mmHg)	125 ± 9	124 ± 10	NS
DBP (mmHg)	72 ± 8	74 ± 8	NS
HR (beats/min)	75 ± 7	73 ± 7	NS
LVEF (%)	35 ± 10	35 ± 9	NS
LVDd (%)	63 ± 8	62 ± 7	NS

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ARB, angiotensin II receptor antagonist. Other abbreviations are the same as in Tables 1 and 2.

DISCUSSION

This is the first study to address the acute effect of an ARB, valsartan on the development of TWA in patients with CHF who are at risk of SCD. Findings showed that short-term oral administration of valsartan markedly reduced TWA power and increased OHR. These ARB-mediated acute effects of improving repolarization abnormality might provide useful information about the arrhythmogenic substrate for malignant ventricular arrhythmias.

Comparisons with previous work. Suppressing the development of ventricular repolarization alternans may lead to the prevention of SCD related to VT/VF. In this regard, antiarrhythmic agents such as procainamide (18), *d,l*-sotalol (19), and β -blocker (20) have been clinically tested in terms of their effects on ventricular repolarization alternans as detected by TWA testing in the acute setting.

However, these agents do not always have the long-term outcome of reducing SCD incidence. Indeed, although having an acute beneficial effect on TWA, procainamide is not conclusively appropriate for long-term therapy in light of the Cardiac Arrhythmia Suppression Trial (CAST) (21) findings. The reduction of TWA produced by *d,l*-sotalol, a β -blocker with additional class III antiarrhythmic properties, appears to be mainly attributable to the action of β -blockade. Of agents that have a beneficial effect on TWA in the acute setting, widely-recognized evidence of long-term reduction in mortality from SCD in large-scale clinical trials is only available for β -blockers (22-24). Moreover, amiodarone was also shown to have a favorable effect on repolarization alternans (25). However, although having been proposed to be effective in suppressing ventricular arrhythmias as well as in reducing the mortality in patients with CHF (26, 27), amiodarone did not improve the survival from SCD in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (28). These results suggest that the β -adrenergic system might be a critical regulator of ventricular repolarization alternans and a key determinant of SCD.

In addition to the β -adrenergic system, the RAS plays an important role in the pathophysiology of cardiovascular diseases. Accumulated clinical evidences of reducing mortality due to the reduction of SCD of ACE-Is in addition to their known hemodynamic benefits have led to increased use of this agent in patients with CHF and VT (29, 30). Moreover, ARB has been suggested to possess comparable beneficial effects on symptoms and survival in patients with CHF. In the ELITE trial (31), one such agent, losartan, was shown to have long-term benefit of reducing overall mortality 46% compared to captopril in patients with symptomatic heart failure and left ventricular systolic dysfunction. It is noteworthy that most of this difference in mortality was attributable to 64% reduction in the incidence of SCD in the losartan group. In the present study, valsartan-mediated improvement of ventricular repolarization abnormality was achieved in a short-term of 3 days. This result suggests that valsartan may have the acute effect of correcting the electrophysiological arrhythmic substrate of the ventricle, and which may partially contribute to the superiority of losartan in the reduction of SCD in the ELITE trial.

Potential therapeutic target for preventing SCD. Pharmacologically, the CAST (21) study, which was solely aimed at suppressing premature ventricular contractions that trigger VT/VF, has led us to reconsider optimal antiarrhythmic therapy; although Class I antiarrhythmic agents had remarkable efficacy against premature ventricular contraction, and unfortunately resulted in increased mortality from SCD. Moreover, amiodarone, which seemed to be potentially beneficial in Class III antiarrhythmic agents, failed to improve survival from SCD compared to the subjects for control in the SCD-HeFT (28). Hence, a new approaching pharmacological therapeutic target in terms of mechanism- and disease-specific fashion is required.

Recently, theoretical and experimental studies have proposed that ventricular repolarization alternans (i.e. action potential duration (APD) alternans) acts as a triggering mechanism leading to the initiation of VT/VF (1, 2). Even in the normal ventricle, the distribution of APD is heterogeneous spatially from base to apex (32, 33) and transmurally among the epicardial, M cell, and endocardial regions (34). Moreover, enhancement of these heterogeneities in a heart-rate-dependent manner causes APD to alternate beat-to-beat between long and short APDs. This dynamic fluctuation of APD generates electrical instability of the ventricle. APD alternans, particularly the discordant form, can cause spatial repolarization gradients steep enough to produce unidirectional conduction block and subsequent initiation of VT/VF. Discordant APD alternans was elicited for the first time throughout the epicardial ventricle of normal guinea pig hearts by Pastore *et al* (1).

ACUTE EFFECTS OF ARB ON TWA

Subsequently, Shimizu et al. observed transmural discordant alternans between the epicardial and M cell regions in structurally normal dog ventricles under conditions electrophysiologically mimicking congenital those of long-QT3 syndrome (35). Accordingly, the dynamics of ventricular repolarization might represent a new potential therapeutic target.

In the present study, valsartan had the effect of attenuating the development of ventricular repolarization alternans detected by TWA measurement, and this may show considerable promise of ARB as a new approaching prophylactic arrhythmic therapy of suppressing the arrhythmogenic substrate for malignant ventricular arrhythmias. It is anticipated that this could lead to the further development of a new effective antiarrhythmic drug targeted at these mechanisms.

Possible mechanism of ARB for improving TWA and OHR. Both experimentally and clinically, the relationship between TWA and OHR has been well-established. TWA can be induced either by pacing or by elevating heart rate with exercise. Patients with normal cardiac function often exhibit TWA at heart rates ≥ 120 bpm, while those at risk of SCD exhibit TWA at heart rates ≤ 110 bpm (36). Furthermore, our group has reported that patients with dilated cardiomyopathy in whom TWA occurs at OHR of ≤ 100 bpm exhibit a high incidence of malignant ventricular arrhythmia (10).

The present study demonstrates that valsartan increased the OHR of TWA to over 100 bpm in patients with CHF. The mechanism of this effect, along with that of TWA reduction, may reflect valsartan-mediated modification of APD restitution property. APD restitution, defined as the relationship between APD and the diastolic interval preceding it, is displayed as a curve, and the slope of which is suggested to be an important determinant of APD alternans. When the slope of the APD restitution curve exceeds 1, alternans occurs between beat-to-beat long and short APDs (37, 38). We speculate that critical HR, corresponding to the point where the slope of the APD restitution curve exceeds 1, can be assumed to be the OHR of TWA and thus the OHR of TWA is essentially determined by the slope of the APD restitution curve. Our findings suggest that the slope of the greater part of the curve corresponding to the HR range from resting to 110 bpm may be steep in patients with positive TWA. This slope of the restitution curve can be influenced by changing the kinetics of membrane currents. Although various ion channels are involved, I_{Ca} has been suggested to be the major contributor for regulating the slope of the curve and the enhancement of I_{Ca} can steepen the slope. Accumulated data suggest that Ang II affects membrane currents including I_{Ca} in the failing heart (39, 40). Valsartan may flatten this slope by blocking the pathophysiological effects of Ang II, thereby shifting the OHR to TWA towards the upper heart rate, and contributing to the reduction of TWA voltage.

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ACUTE EFFECTS OF ARB ON TWA

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