T Wave Alternans for Predicting Adverse Effects of Amiodarone in a Patient With Dilated Cardiomyopathy

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An implantable cardioverter defibrillator (ICD) was used in a 62-year-old man with dilated cardiomyopathy (DCM) because of hemodynamically intolerable ventricular tachycardia (VT). Amiodarone was administered after a second episode of ICD discharge. Three weeks later, incessant VT appeared, and DC discharge failed to terminate it. Microvolt T wave alternans (TWA), measured by a spectral method, was observed in this patient with and without amiodarone administration. The onset heart rate with TWA was lower and the alternans voltage was higher with amiodarone than without it. The effects of amiodarone appeared to be related to the exacerbation of VT and an increased defibrillation threshold. TWA might be useful in predicting the proarrhythmic effects of amiodarone in similar cases. (*Jpn Circ J* 2001; 65: 468–470)

Key Words: Implantable cardioverter defibrillator; Proarrhythmic effect; Ventricular tachycardia

Amiodarone has been reported to reduce overall mortality and morbidity in patients with non-ischemic cardiomyopathy, but it has not improved the frequency of sudden cardiac death in such patients.^{1,2} It is not clear why this should be, but it is possibly related to the proarrhythmic effects of amiodarone.^{3–6} It was recently reported that the implantable cardioverter defibrillator (ICD) is more effective than antiarrhythmic agents, amiodarone in particular, in preventing sudden cardiac death in patients with left ventricular dysfunction.⁷ Some authors have noted that amiodarone can increase the defibrillation threshold.^{8,9} Rosenbaum et al showed that microvolt T wave alternans (TWA) is a promising predictor of vulnerability to ventricular tachyarrhythmia.¹⁰ Previous studies have demonstrated that the magnitude of TWA is dependent on heart rate.¹¹ In addition, Tanno et al have reported that TWA that appears at a rate of less than 100 beats/min is closely related to ventricular tachyarrhythmia.¹² We hypothesized that when the onset heart rate of TWA is lowered after administration of drugs, the risk of the proarrhythmic effects of those drugs is increased.

Case Report

A 62-year-old man with dilated cardiomyopathy (DCM) and paroxysmal atrial fibrillation was admitted to hospital in May 1998 because of palpitations caused by sustained ventricular tachycardia (VT), though he had been taking methyl digoxin (0.1 mg/day) and pirfenolol (150 mg/day) for

2 years. On physical examination, blood pressure was 78/–mmHg; and pulse rate was 180 beats/min and regular. The electrocardiogram (ECG) showed a wide QRS complex tachycardia exhibiting right bundle branch block and right axis deviation at a rate of 188 beats/min, which was terminated by electrical cardioversion with a 50-J DC shock. The ECG showed conversion to normal sinus rhythm at a rate of 70 beats/min with normal axis and a normal QT interval (QT: 0.44 ms/QTc: 0.48). Chest X-ray showed no sign of pulmonary congestion or cardiomegaly (Fig 1A,B). Laboratory data showed mild elevation of aspartate aminotransferase (60 IU/L), alanine aminotransferase (55 IU/L), and γ -glutamyl transpeptidase (260 IU/L) because of chronic hepatitis C. Two-dimensional echocardiogram showed a severely hypokinetic left ventricle (LV) the dimensions of which were enlarged (LV end-diastolic dimension: 64.9 mm, LV ejection fraction: 29%).

Several forms of sustained VT were induced by programmed ventricular stimulation during an electrophysiologic study. The sustained VTs were hemodynamically unstable, and we had to terminate them with DC cardioversion. An implantable cardioverter defibrillator (ICD) was used because bepridil could not prevent sustained VT. Ten days after the implantation, the VT reappeared and was terminated with 10 J cardioversion. Metoprolol (5 mg/day) was administered in addition to bepridil. However, the VT reoccurred and the ICD discharged twice 2 weeks later. Bepridil was then replaced with amiodarone (200 mg/day) and 3 weeks later, an incessant form of VT appeared that occasionally failed to respond to the ICD at 30 J (Fig 2). Such VT had not occurred before the administration of amiodarone. At this time, the QT interval was slightly prolonged (QT: 0.48 ms/QTc: 0.52). The TWA findings are shown in Fig 3: the alternans voltage was greater than 1.9 μ V in the vector magnitude (VM), Z and V₄ leads at a rate of 100 beats/min, whereas the alternans voltage was

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Fig 1. (A) Chest X-ray on admission shows no sign of congestion; the cardiothoracic ratio (CTR) was 48.8%. (B) ECG after cardioversion shows normal sinus rhythm with a normal axis; the QT interval is normal (QT: 0.44 ms/QTc: 0.48).

Fig 2. Three weeks after amiodarone administration, incessant VT appeared, which sometimes failed to respond to the ICD at 30J.

Fig 3. (A) Alternans voltage is greater than $1.9\mu\text{V}$ in VM, Z, and V4 leads at a heart rate of 100 beats/min during bepridil administration. (B) Alternans voltage is greater than $1.9\mu\text{V}$ in VM, Z, and V4 leads at a heart rate of 70 beats/min during amiodarone administration.

greater than 1.9µV in the same leads at a rate of 70 beats/min 21 days after administration of amiodarone (Fig 3B). We considered the amiodarone was proarrhythmic and that it increased the defibrillation threshold in this case. Therefore it was discontinued and sotalol was administered to the patient at 120mg/day. VT did not recur, and we did not observe a lowering of the onset heart rate of TWA with sotalol. The patient was eventually discharged from the hospital and has remained in a stable condition.

Discussion

Amiodarone is a class III antiarrhythmic drug that is effective in the management of refractory ventricular arrhythmia,¹³ although adverse effects have been reported, including interstitial pneumonia, thyroid dysfunction, corneal disturbance, and proarrhythmia^{3,4} and some of these effects are dose- and time-related.¹⁴ McGovern et al described incessant VT in 5% of patients after 7–35 days of treatment with amiodarone.¹⁵ In the present patient, sustained VT was terminated with electrical cardioversion at 10J before amiodarone was administered, but VT occurred incessantly at 21 days following administration. In addition, the VT sometimes failed to respond to ICD with 30J. Proarrhythmia is the provoking of a new arrhythmia or the aggravation of a pre-existing arrhythmia during therapy with drugs at doses or plasma concentrations below those considered to be toxic.¹⁶ Amiodarone may have been proarrhythmic in this case of incessant VT because the patient had never experienced incessant VT before the treatment with amiodarone, the drug most likely to have increased the defibrillation threshold. To our knowledge, there are not any published reports relating TWA and proarrhythmia. TWA is considered positive when the alternans voltage is >1.9µV with the alternans ratio >3 in the VM lead, any orthogonal lead, or 2 consecutive precordial leads, and the onset heart rate at which TWA is seen is <110 beats/min.^{11,12,17,18} Recordings of TWA were obtained in sinus rhythm with atrial pacing at 70, 80, 90, 100 and 110 beats/min for a minimum of 3 min at each pacing rate or with a bicycle ergometer. Positive TWA was observed in the present patient at lower heart rates during treatment with amiodarone compared with that seen before it was given (drug-free state). The TWA onset heart rate (during atrial pacing) in the drug-free state was 100 beats/min, but after amiodarone administration, the onset heart rate (during exercise) decreased to 70 beats/min. TWA in humans is strongly dependent on heart rate, and TWA in patients with organic heart disease and VT appears at lower heart rates than in patients without VT.¹¹ Thus, it might be that when the TWA onset heart rate is decreased, the vulnerability to VT is increased. In the present patient, 1 month after discontinuing amiodarone the TWA onset heart rate returned to that of the drug-free state, and the incessant VT gradually decreased. The TWA findings and the patient's clinical course suggest that the novel appearance of incessant VT and the increase in defibrillation threshold might be secondary to the adverse effect of amiodarone. Groh et al reported a positive TWA to be significantly less likely in

patients receiving amiodarone than in patients not receiving it.¹⁹ Kavesh et al reported that the magnitude of TWA decreased with another antiarrhythmic agent (procainamide).¹⁷ There have been very few reports of the proarrhythmic effects of amiodarone, or of other antiarrhythmic agents, increasing the magnitude of TWA or lowering the TWA onset heart rate. Therefore, we suggest that the lowering of the TWA onset heart rate is useful for predicting ventricular proarrhythmia when patients are treated with antiarrhythmic agents.

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