Evaluation of Proarrhythmic Effect of Antiarrhythmic Drugs on Ventricular Tachycardia Associated with Congestive Heart Failure

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The usefulness and limitations of antiarrhythmic drugs in ventricular tachycardias (VT) associated with congestive heart failure remain uncertain. The purpose of this study is to evaluate the proarrhythmic effects of antiarrhythmic drugs in patients with refractory VT associated with left ventricular dysfunction using electrophysiologic study (EPS).

Twenty-four patients with left ventricular dysfunction, defined by left ventricular ejection fraction (LVEF) lower than 40% using left ventriculography, were studied. The average LVEF was 29.5%. As for underlying heart disease, 14 had old myocardial infarction, 8 cases had dilated cardiomyopathy and 2 had aortic regurgitation. As a control to this group, 23 cases with underlying heart disease and LVEF higher than 40%, and 27 cases with no obvious heart disease were studied. We considered a drug to have proarrhythmic effects if 1) it decreased by one the number of stimuli needed to induce VT, 2) induced non-sustained VT in the control study which changed to induced sustained VT, 3) the sustained VT or ventricular fibrillation was newly induced, or 4) the induced sustained VT which was stopped by pacing in the control study changed to induced VT which could not be terminated by pacing and required DC shock. Proarrhythmic effects were recognized in 17 of 24 cases with left ventricular dysfunction. Of the 67 drug trials, proarrhythmic effects were seen in 26. Proarrhythmias were observed in 9 of 23 cases (39.1%) with organic heart disease associated with LVEF higher than 40%. In 12 of 69 drug trials (17.4%) proarrhythmias were observed. Of 27 cases with no obvious heart disease 10 cases (37%) had proarrhythmias. In 14 of 130 drug trials (10.8%), proarrhythmias were recognized.

In conclusion, the incidence of ventricular arrhythmias on EPS in cases with low LVEF was 70.8%, and 33.8% in drug trial, higher than in cases with organic heart disease and LVEF higher than 40%. Although the relation to spontaneous occurrence is not always clear, the effects of antiarrhythmic drugs therapy on ventricular arrhythmias in patients with congestive heart failure needs careful consideration and should be an interesting topic for future research.

(*Jpn Circ J* 1992; 56: 69–76)

VENTRICULAR arrhythmias are frequently observed in patients with congestive

Key words:

Ventricular tachycardia
Congestive heart failure
Antiarrhythmic drug
Proarrhythmic effect
Electrophysiologic study

heart failure. Their mortality rate has been high and half the deaths have been due to sudden cardiac death^{1–4}. Ventricular tachycardia (VT) might be a risk factor for sudden cardiac death⁵. Therefore, it is very important to know the pathogenesis of ventricular

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TABLE I THE INCIDENCE OF PROARRHYTHMIC EFFECT OF ANTIARRHYTHMIC DRUGS IN 24 CASES WITH UNDERLYING HEART DISEASES ASSOCIATED WITH LVEF $\leq$ 40%, IN 23 CASES WITH UNDERLYING HEART DISEASE ASSOCIATED WITH LVEF $>$ 40%, IN 23 CASES WITH NO OBVIOUS HEART DISEASE

	Case	Drug test
LVEF $\leq$ 40%	17/24 (70.8%)	26/67 (33.8%)
old myocardial infarction	9/14 (64.3%)	13/40 (32.5%)
LVEF $>$ 40%	9/23 (39.1%)	12/69 (17.4%)
old myocardial infarction	3/8 (37.5%)	2/14 (14.3%)
no obvious heart disease	10/27 (37.0%)	14/130 (10.8%)

arrhythmias associated with congestive heart failure, and know how to treat ventricular arrhythmias. Although recent advances in antiarrhythmic drug therapy for refractory ventricular arrhythmia are significant, antiarrhythmic drugs also generally aggravate and provoke ventricular arrhythmias (so-called proarrhythmic effects)⁶⁻¹⁰ and result in negative inotropic effects!¹¹ Therefore, usefulness and limitations of antiarrhythmic drugs in ventricular arrhythmias associated with congestive heart failure remains unknown.

The purpose of this study is to evaluate the proarrhythmic effects of antiarrhythmic drugs in patients with refractory VT associated with left ventricular dysfunction using electrophysiologic study (EPS).

MATERIALS AND METHOD

Materials: Twenty of our patients with refractory VT, associated with left ventricular dysfunction, (defined as left ventricular ejection fraction (LVEF) lower than 40% using left ventriculography) were studied. Twenty-three patients were male and 1 was female. They ranged in age from 39 to 69 years, average age being 58.1. The average LVEF was 29.5%, with a range from 5 to 40%. The average cardiothoracic ratio was

53%, range 48 to 69%. Digitalis and diuretics were administered in 21 of 24 cases (87.5%). 20 cases had sustained VT and 4 had non-sustained VT. As for underlying heart disease, 14 cases had old myocardial infarction, 8 cases had dilated cardiomyopathy, and 2 cases had aortic regurgitation.

As a control to the above, 23 cases with underlying heart disease and LVEF higher than 40% were used (19 male, 4 female), their average age being 38.6. Eight of these cases had old myocardial infarction (all male), their average age being 24.8. Also used for reference with 27 cases with no obvious heart disease (22 male, 5 female) their average age being 34.1.

Method: Programmed electrical stimulation was performed with a specifically designed programmable stimulator (San-ei Sokki)¹² The electrical stimulation protocol consisted of single, double, and triple extra-stimuli during paced rhythm, whose basic cycle lengths were 600, 500, and 400 ms; rapid pacing and burst pacing. The site of stimulation was the apex and the outflow tract of the right ventricle. Antiarrhythmic drugs were discontinued for a period of 4 drug half-lives prior to the test. Following control studies, serial tests were performed after intravenous administration of the following: procainamide 400–1000 mg iv, disopyramide 250–1000 mg iv, cibenzoline, lidocaine 50–100 mg iv, mexiletine 50–125 mg iv, propafenone 50–100 mg iv, flecainide 50–100 mg iv, verapamil 5–10 mg iv, bepridil 200 mg po, amiodarone 200–400 mg po, and E-4031 6–9 μ g/kg iv.

A total of 67 drug tests were performed, in 24 cases with left ventricular dysfunction, and 69 drug tests were performed in 23 cases with LVEF higher than 40% and underlying heart diseases. One-hundred-thirty drug tests were performed in 27 cases with no obvious heart disease.

We evaluated the proarrhythmic effect of the drugs by the following. We considered that a drug had proarrhythmic effects if 1) it decreased by one the number of stimuli needed to induce VT, 2) the sustained VT or ventricular fibrillation was newly induced, 3) induced non-sustained VT in the control study changed to induced sustained VT after administration of the drug or 4) the induced

Fig. 1. A typical case, 49 y, male, old myocardial infarction, sustained VT, LVEF 39.0%, in which it decreased by one the number of stimuli needed to induce VT. In the control study (A), sustained VT could be induced by double extrastimuli.

Fig. 2. A typical case, male, 64 y, old myocardial infarction, sustained VT, LVEF 23.2%, in which VT was newly induced. In the control study (A), VT could not be induced by programmed stimulation including triple extrastimuli at the apex and outflow tract of right ventricle. After administration of aprindine (B), sustained monomorphic VT could be induced by double extrastimuli at the apex of RV and could be terminated by burst pacing.

sustained VT which terminated spontaneously or was stopped by pacing in the control study changed to induced VT which could not be terminated by pacing and required DC shock.

Sustained VT was defined as VT that lasted for over 30 sec and required either drugs, pacing or DC cardioversion for termination. Non-sustained VT was defined as VT with a duration greater than 10 complexes, while spontaneously terminating within 30 sec.

RESULTS

1. Proarrhythmic effect of agents in 24 cases with left ventricular dysfunction (Table I).

Proarrhythmic effects were recognized in 17 of 24 cases (70.8%). Of the 67 drug tests, 26 demonstrated proarrhythmic effects. In underlying heart disease patients, effects were observed in 9 of 14 cases with old myocardial infarction and in 13 of 40 drug tests (32.5%), in 8 of 10 cases with cardiomyopathy or valvular heart disease and in 13 of 27 drug tests (48.1%).

Figures 1, 2, 3, and 4 show a typical case, in which the criteria for proarrhythmic effect were fulfilled. Decrease of the number of extrastimuli was observed in 10 cases (41.7%), new induction of VT in 4 cases (20.8%), changes to the induced sustained

Fig. 3. A typical case in which induced nonsustained VT in the control study changed to induced sustained VT. He was 57 y and had dilated cardiomyopathy and sustained VT. LVEF was 23.6%. In the control study (A) non-sustained monomorphic VT induced by double extrastimuli at the outflow tract of RV. After administration of mexiletine, sustained VT could be induced by double extrastimuli at the apex of RV. VT could be terminated by DC shock.

Fig. 4. A typical case, 65 y, male, old myocardial infarction, sustained VT, LVEF 38.0%, in which difficulty of VT termination was observed. In the control study (A), sustained VT could be induced by double extrastimuli and could be easily induced by burst pacing. After administration of mexiletine, induced sustained VT could not be terminated by burst pacing resulting in acceleration of VT, and required DC shock.

TABLE II BREAKDOWN OF THE CRITERIA EXHIBITED FOR ARRHYTHMIAS AND THE CRITERIA ACCORDING TO ANTIARRHYTHMIC DRUGS IN 24 CASES WITH LVEF>40%

<i>Total case Drug</i>	<i>Decrease of number of extrastimuli</i>	<i>New induction of VT</i>	<i>Changes to induced sustained VT</i>	<i>Difficulty of VT termination</i>
	<i>10 cases (41.7%)</i>	<i>5 cases (20.8%)</i>	<i>12 case (50.0%)</i>	<i>4 cases (16.6%)</i>
<i>Class IA (10 tests)</i>	<i>2 (20.0%)</i>		<i>1 (10.0%)</i>	
<i>Class IB (24 tests)</i>	<i>3 (12.5%)</i>	<i>4 (16.6%)</i>	<i>8 (33.3%)</i>	<i>4 (16.6%)</i>
<i>Class IC (10 tests)</i>	<i>2 (20.0%)</i>		<i>1 (10.0%)</i>	
<i>Class III (19 tests)</i>	<i>3 (15.8%)</i>	<i>1 (5.2%)</i>	<i>1 (5.2%)</i>	
<i>Class IV (4 tests)</i>			<i>1 (25.0%)</i>	

TABLE III PROARRHYTHMIC EFFECTS OF RESPECTIVE ANTIARRHYTHMIC AGENTS

	<i>Proarrhythmia</i>		<i>Proarrhythmia</i>
<i>Class IA agents (10 tests)</i>	<i>30.0%</i>	<i>procainamide (6) disopyramide (3) cibenzoline (1)</i>	<i>2 tests 1 test 0</i>
<i>Class IB agent (24 tests)</i>	<i>58.3%</i>	<i>mexiletine (18) aprindine (5) tocainide (1)</i>	<i>9 tests 5 tests 0</i>
<i>Class IC agent (10 tests)</i>	<i>30.0%</i>	<i>propafenone (2) flecainide (8)</i>	<i>1 test 2 tests</i>
<i>Class III agent (19 tests)</i>	<i>26.3%</i>	<i>amiodarone (14) E4031 (4)</i>	<i>5 tests 0</i>
<i>Class IV agent (4 tests)</i>	<i>25.0%</i>	<i>verapamil (3) bepridil (1)</i>	<i>1 test 0</i>

VT in 12 cases (50.0%), and difficulty of VT termination in 4 cases (16.6%). In cases with old myocardial infarction these criteria were recognized in 5 cases, 1 cases, 6 cases, and 3 cases, respectively.

As for breakdown of criteria according to antiarrhythmic agents (Table II), decrease in the number of stimulations needed to induce VT was observed in 12.5–20.0% of patients given class IA, IB, IC, and III agents.

VT was newly induced by class IB agents in 16.6%, and class III agents in 5.2%. The nonsustained VT with control study changed 33.3% to sustained VT after administration of class IB agents, 25.0% in class IV agents, 10.0% for class IA agents and in class III agents, 5.2%.

The 16.6% whose VT was induced after administration of class IB agents required DC shock. 4 cases had 2 or more proarrhythmias, which were induced by class IB agents.

2. Proarrhythmic effects of respective antiarrhythmic agents (Table III).

All antiarrhythmic agents except for cibenzolin, tocainide and bepridil, (which was administered in only one case), and E4031, had some proarrhythmic effects. Aprindine led to proarrhythmia in all 5 cases, mexiletine in 9 of 18 cases, procainamide in 2 of 6 cases, disopyramide in 1 of 3 cases, flecainide in 2 of 8 cases, propafenone in 1 of 2 cases, amiodarone in 5 of 14 cases and vera-

pamil in 1 of 3 cases. As for Vaughan Williams' classification, the incidence of proarrhythmia was 30.0% in class IA agents, 58.3% in class IB agents, 30.0% in class IC agents, 26.3% in class III agents, and 25% in class IV agents.

3. *Proarrhythmic effects of agents in 23 cases with underlying heart disease and LVEF higher than 40% and in 27 cases with no obvious heart disease.*

Proarrhythmias were observed in 9 of 23 cases with organic heart disease associated with LVEF higher than 40%. In 12 of 69 drug tests (17.4%), proarrhythmias were observed. In 3 of 8 cases (37.5%) with old myocardial infarction and LVEF higher than 40%, proarrhythmias were observed. In 2 of 14 drug tests, proarrhythmias were observed. Of 27 cases with no obvious heart disease, 10 cases (37%) had proarrhythmias. In 14 of 130 drug tests (10.8%), proarrhythmias were recognized (Table I).

DISCUSSION

1. *Evaluation of proarrhythmic effects of antiarrhythmic drugs in patients with heart failure using EPS.*

There are many factors aggravating and provoking ventricular tachyarrhythmia in congestive heart failure, such as left ventricular LV dysfunction, myocardial damage, catecholamines, activity of the renin-angiotensin system, electrolyte abnormalities (especially low potassium and magnesium), and various drugs (such as digitalis, catecholamines, and diuretics)¹³ Proarrhythmias due to antiarrhythmic drugs are classified into 2 groups: secondary proarrhythmias, (which have some predisposing factors such as increases of serum drug concentration, combined drugs, electrolyte abnormalities, myocardial ischemia, etc.), and primary proarrhythmia (which have no predisposing factors). In patients with congestive heart failure, the incidence of secondary proarrhythmia increased because of presence of the primary factors noted above. Furthermore, primary proarrhythmia was also common because of the presence of the substrate due to damaged myocardium, resulting in the high incidence of proarrhythmia due to antiarrhythmic drugs.

Although the pathophysiology, mechanism, incidence, diagnosis, clinical significance, and therapy of proarrhythmia in cases with congestive heart failure remains unclear, it is very important to evaluate and predict the proarrhythmic effects of antiarrhythmic drugs.

It is difficult to differentiate proarrhythmias due to drug effects on arrhythmia aggravation and induction, day to day variability, progression of pathophysiology, and the addition of new predisposing factors such as low potassium and myocardial ischemia etc. We cannot evaluate the reproducibility of proarrhythmias because of medical problems such as severity of ventricular arrhythmia and heart failure possibly resulting in death, and other ethical problems. Recently much interest has focussed on the evaluation of proarrhythmia using EPS^{8,14-19} and Holter ECG^{9,20-21}

EPS is considered to be more useful than Holter ECG because of reasons mentioned previously. The criteria describing proarrhythmia using EPS has not been established yet. We considered 4 criteria for proarrhythmia: decreases of single extrastimuli to induced VT, new induction of VT, changes from non-sustained VT to sustained VT, and a difficulty of VT termination.

We considered a proarrhythmic effect to be that which required more than one stimuli to induce VT. However Poser et al¹⁷ proposed a different criterion of extrastimuli required to induce VT after administration of agents. Although induction of VT at faster rates during drug therapy has been considered to be a proarrhythmic effect in other reports,¹⁷ we did not consider this to be so because VT with several rates were induced during EPS.

These criteria of proarrhythmia identification through EPS should be evaluated extensively and long term studies should be commenced in the near future to indicate whether or not patients showing this response have an increased probability of spontaneous arrhythmias during follow up.

2. *Proarrhythmia in patients with and without low LVEF.*

The incidence of ventricular proarrhythmias has been reported at 23 to 39% of cases and 11 to 26% of drug tests¹⁴⁻¹⁹ It has been

pointed out that the incidence is higher in patients with sustained VT or ventricular fibrillation, underlying heart disease, and LV dysfunction. Podrid et al¹⁰ compared proarrhythmias in cases with LVEF higher than 35% and LVEF lower than 35%. In the former, the incidence of proarrhythmias was 26% in cases, and in the latter, it was 43%. In our study, we compared cases above and below 40% LVEF, and found proarrhythmias in 39.1% of cases, and in 17.4% of drug tests in the former, and in 70.8% of cases, and 33.8% of drug tests in the latter. The reason incidences were higher in both of our cases may be due to differences of subjects, stimulation protocol and criteria of proarrhythmia. Of cases with underlying heart disease with LVEF over 40%, the incidence is 37% in cases and 39.1% in drug tests. Looking exclusively at 22 cases with old myocardial infarction, 37.5% of cases and 14.3% of drug tests in the former, and 64.3% of cases and 32.5% of drug test in the latter had proarrhythmias. Therefore, LV function was thought to be a more significant risk factor for proarrhythmia than the presence of underlying heart disease. In cases without obvious heart disease, it was 37.0% cases and 10.8% in drug tests, which is not much different than cases with underlying heart disease and over 40% LVEF. Thus, the presence of underlying heart disease was considered to be a less significant factor for proarrhythmias. This is in contrast to earlier reports indicating that proarrhythmias were 2 to 3 times higher in cases with underlying heart disease.^{10,21,22} The reason for this difference is unclear and must be examined.

3. *Criteria of proarrhythmia in cases with low LVEF.*

As for criteria of proarrhythmia, the incidence of decrease of extrastimuli has been reported to be 6 to 12.0%, that of changes from non-sustained VT to sustained VT 1.8 to 13.7%, newly provoked VT 2%, and difficulties of VT termination and acceleration of VT 5.9%. In our study, the incidence is 14.9%, 17.9%, 7.4% and 6.0%, respectively. Poser et al¹⁷ differentiated definite criteria, which were decrease of 2 extrastimuli, changes to sustained VT, (newly provoked VT or induction of VF), and possible criteria, which were decrease of 1 single sti-

mus and difficulties of VT termination.

They reported that their incidences were 3.7%, 9.2%, 2.3%, and 0.9%, respectively. Few studies of the detailed criteria for proarrhythmia in cases with low LVEF have been reported.

4. *Proarrhythmic effects of respective antiarrhythmic drugs.*

Ventricular proarrhythmias are induced by all antiarrhythmic drugs. The incidence varies widely from 5 to 33%.¹⁶⁻¹⁹ The reason for such broad variations in reports may be due to the criteria, subjects' arrhythmias, underlying heart disease and LV function. In our study, the incidence was 0 to 100%, however, our patient numbers was small. Class IB agents had greater proarrhythmic effects due perhaps to their use in patients with more LV dysfunction. It must be cautioned that class IB agents, especially aprindine, have less negative inotropic effects, and even higher proarrhythmia effects on EPS. And class IB agents may allow VT to be induced more easily while making it more difficult to terminate. The mechanism might be due to conduction suppression effects and shortening of refractory periods. Further evaluation of proarrhythmic effects of respective antiarrhythmic agents are required.

Recently, amiodarone has been the focus of much attention as the last-choice drug for cases with refractory VT associated with CHF.²³ In our study, even amiodarone had 35% proarrhythmic effects. Although EPS was thought to be less useful in evaluating the efficiency of amiodarone, these effects should be kept in mind.

In conclusion, the incidence of ventricular proarrhythmia on EPS in our study for cases with LVEF less than 40% was significantly higher compared to that in cases with LVEF higher than 40%. Although the relation to its spontaneous occurrence is not always clear, it is thought to be clinically important. Furthermore, antiarrhythmic drugs have more or less negative inotropic effects. On the other hand, the main cause of sudden death in patients with congestive heart failure has been thought to be ventricular tachyarrhythmias. Therefore, therapy of antiarrhythmic drugs on ventricular tachyarrhythmias in patients with congestive heart

failure needs careful consideration and should be a vital topic of future research.

REFERENCES

1. McFATE SMITH, W: Epidemiology of congestive heart failure. *Am J Cardiol* 1985; **55**: 3A
2. MASSIE, BM et al: Survival of patients with congestive heart failure: Past, present and future prospects. *Circulation* 1987; **75** (Suppl IV): 11
3. BIGGER JT: Why patients with congestive heart failure die: Arrhythmia and sudden cardiac death. *Circulation* 1987; **75** (Suppl IV): 28
4. BIGGER Jr., JT: Relation between left ventricular dysfunction and ventricular arrhythmias after myocardial infarction. *Am J Cardiol* 1986; **57**: 8B
5. GRADMAN, A. et al: Predictors of total mortality and sudden death in mild to moderate heart failure. *J Am Coll Cardiol* 1989; **14**: 564
6. CAMPBELL, RWF: Arrhythmogenesis: A European Perspective. *Am J Cardiol* 1987; **59**: 49E
7. HOROWITZ, LN, et al: Proarrhythmia, arrhythmogenesis, or aggravation of arrhythmia: A status report, 1987. *Am J Cardiol* 1987; **59**: 54E
8. BIGGER JT, et al: Clinical types of proarrhythmic response to antiarrhythmic drugs. *Am J Cardiol* 1987; **59**: 2E
9. VELEBIT V, et al: Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation* 1982; **65**: 886
10. PODRID PJ, et al: Aggravation of arrhythmia by antiarrhythmic drugs-Incidence and predictors. *Am J Cardiol* 1987; **59**: 38E
11. RAVID S et al: Congestive heart failure induced by six of the newer antiarrhythmic drugs. *J Am Coll Cardiol* 1989; **14**: 1326
12. KASANUKI H, et al: Availability of electrophysiological approach to the selection and assessment of antiarrhythmic drugs for recurrent ventricular tachycardia. *Jpn Circ J* 1983; **47**: 105
13. PARMLEY WW et al: Factors causing arrhythmias in chronic congestive heart failure. *Am Heart J* 1987; **114**: 1267
14. BUCHALTER M, et al: Arrhythmogenesis and programmed stimulation techniques. *Eur Heart J* 1988; **9** (Suppl B): 13
15. HOROWITZ LN, et al: Proarrhythmic responses during electrophysiologic testing. *Am J Cardiol* 1987; **59**: 45E
16. TORRES V, et al: The arrhythmogenicity of antiarrhythmic agents. *Am Heart J* 1985; **109**: 1090
17. POSER RP, et al: Aggravation of arrhythmia induced with antiarrhythmic drugs during electrophysiologic testing. *Am Heart J* 1985; **110**: 9
18. RAE AP, et al: Proarrhythmic effects of antiarrhythmic drugs in patients with malignant ventricular arrhythmias evaluated by electrophysiologic testing. *J Am Coll Cardiol* 1988; **12**: 131
19. AU PK, et al: Proarrhythmic effects of antiarrhythmic drugs during programmed ventricular stimulation in patients without ventricular tachycardia. *J Am Coll Cardiol* 1987; **9**: 389
20. MORGANROTH J, et al: Application of a frequency definition of ventricular proarrhythmia. *Am J Cardiol* 1987; **59**: 97
21. MORGANROTH J: Risk factors for the development of proarrhythmic events. *Am J Cardiol* 1987; **59**: 32E
22. SLATER W, et al: Clinical predictors of arrhythmia worsening by antiarrhythmic drugs. *Am J Cardiol* 1988; **61**: 349
23. GREENE HL: The efficacy of amiodarone in the treatment of ventricular tachycardia or ventricular fibrillation. *Prog Cardiovasc Dis* 1989; **31**: 319