Availability of Electrophysiological Approach to the Selection and Assessment of Antiarrhythmic Drugs for Recurrent Ventricular Tachycardia

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We performed serial electrophysiological-pharmacological studies on 21 patients with recurrent sustained or non-sustained ventricular tachycardia (VT). In 8 of 11 patients with recurrent sustained VT, VT could be induced repeatedly by programmed electrical stimulation and terminated by ventricular burst pacing. In 13 of the 21 patients, repetitive ventricular response (RVR) was successfully induced. In the 8 patients with induced VT, the efficacy of several antiarrhythmic drugs intravenously administered was assessed. Procainamide prevented the initiation of VT in 57%, disopyramide in 50% and mexiletine in 40%. However, lidocaine, propranolol and verapamil could not prevent VT in any of 5, 3 and 6 patients, respectively. Verapamil in combination with quinidine prevented the initiation of VT in one case. Each of disopyramide, propranolol and verapamil increased the VT zone in 2 patients. The drugs belonging to the same group classified by their electrophysiological properties were not interchangeable in 2 patients. Their ability to terminate induced VT did not always correlate with that to prevent its initiation in 2 patients. The effects of specific drugs were rather variable and unpredictable in each patients, and especially those of combination regimens using more than 2 antiarrhythmic drugs were more unpredictable. In all patients, the induced VT was morphologically identical to the spontaneously occurring VT and its rate was ranged within 13% of that of the spontaneously VT. In 10 of 13 patients with RVR, QRS configuration of RVR was not similar to the spontaneously occurring arrhythmia. The pharmacological suppression of RVR as an index for prevention against spontaneous VT remains controversial. This study concludes that the serial electrophysiological-pharmacological study provides a rapid prediction of effectiveness of a particular regimen and combination and a rapid identification of the deleterious effects of certain drugs in patients with recurrent sustained VT.

Key Words:

Recurrent ventricular tachycardia
Electrophysiological-pharmacological testing
Antiarrhythmic drugs
Induced ventricular tachycardia
Repetitive ventricular response

VENTRICULAR tachycardia (VT) is a life threatening ventricular arrhythmia,¹⁻³ inducing hemodynamic deterioration, Adams-Stokes' attack and ventricular fibrillation. Diagnosis and therapy of bradyarrhythmias and supraventricular tachyarrhythmias have been advanced recently⁴ but, those of VT, i.e., the

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Fig. 1. The protocol of serial electrophysiological-pharmacological testing.

clarification of the mechanism of VT, the development of new potential antiarrhythmic drugs, the application of pharmacokinetics and pharmacodynamics, and the trial application of pacemaker and surgical therapy, have just begun.⁵⁻¹¹

The recurrent sustained VT, frequently unsuccessfully treated, makes doctors annoyed. It is difficult how to choose effective regimens, how to determine their dose and an administration interval, and how to evaluate efficacy of the particular drugs, since the attacks suddenly and infrequently occur in many patients, and are not related to the Lown's grade of premature beats in some patients. The medical therapy has been based on empiric choice.

Recently Horowitz et al.¹² and Mason and Winkle¹³ have presented an evaluation method for a drug efficacy, in which VT was provoked by electrical stimulation. This method is considered to be provocative-objective technique. Considerable interest has been generated to this method, which is able to select effective regimens and to treat VT prophylactically.¹²⁻²⁵ However, this approach is controversial, because it is necessary to provoke of a potentially fatal arrhythmia, and the usefulness and limitation of this method has not been established as yet.

The purpose of our present study is to evaluate the electrophysiological-pharmacological method for the selection and assessment of anti-

TABLE I THE INDUCTION AND THE TERMINATION METHODS OF VT BY PROGRAMMED ELECTRICAL STIMULATION

Case	Induction						Termination	
	RA		RV				RV	
	Single	Overdrive	Single	Double	Overdrive	Burst	Single	Burst
1	—	—	—		○	○	—	●
2	—	—	—	○	—		—	●
3	○	○	—		—		—	●
4	—	—	○		—		—	●
5	—	—	—	—	○	○	—	●
6	—	—	○		—		—	●
7	—	—	—		○		—	●
8	—	—	—		○	○	—	●

The open circles show the ability to induce VT and the filled circles show the ability to terminate VT.

TABLE II CLINICAL FEATURES AND ECG FINDINGS OF SPONTANEOUSLY OCCURRED VT AND INDUCED VT IN 8 PATIENTS

Case	Age	Sex	Basic disease	Resting ECG	Spontaneous VT		Induced VT	
					QRS pattern	Rate (/min)	QRS pattern	Rate (/min)
1	58	m	(—)	normal	RBBB + LAD	125	RBBB + LAD	130
2	45	m	Myocard infarction	QS	RBBB + RAD	170	RBBB + RAD	138
3	33	m	(—)	IRBBB	RBBB + LAD	210	RBBB + LAD	182
4	35	m	(—)	normal	LBBB	200	LBBB	194
5	40	m	(—)	normal	LBBB	230	LBBB	190
6	27	m	(—)	normal	RBBB + LAD	170	RBBB + LAD	168
7	30	m	(—)	normal	RBBB + LAD	190	RBBB + LAD	200
8	50	m	AR	IVCD	LBBB	124	LBBB	120

m = male, IRBBB = incomplete right bundle branch block, IVCD = intraventricular conduction disturbance, RBBB = right bundle branch block, LBBB = left bundle branch block, LAD = left axis deviation, RAD = right axis deviation, AR = aortic regurgitation

arrhythmic drugs to recurrent sustained VT and non-sustained VT.

MATERIALS AND METHODS

Materials

Thirty-six patients (22 males and 14 females) with sustained VT or non-sustained VT were studied. They ranged in age from 13 to 71 years, and their average age was 38. Eleven patients with recurrent sustained VT and 10 with non-sustained VT underwent serial electrophysiological studies to test the efficacy of several antiarrhythmic drugs. The effect of drugs on

spontaneous sustained VT was studied in 28 patients. Sustained VT was defined as tachycardia that required antiarrhythmic drugs, or pacing or electrical countershock for its termination. Non-sustained VT was defined as tachycardia that persisted for at least 5 beats and reverted to the sinus rhythm spontaneously within 100 beats. The studies were performed after an informed consent was obtained in the non-sedated, postabsorptive stage.

Methods

Electrophysiological studies were performed using multiple electrode catheters inserted

TABLE III THE PREVENTIVE EFFECT OF SEVERAL ANTIARRHYTHMIC DRUGS AGAINST INDUCED VT IN EIGHT PATIENTS

Case	Drug					
	Group IA		Group IB		Group II	Group IV
	Procainamide	Disopyramide	Lidocaine	Mexiletine	Propranolol	Verapamil
1	⊙	⊙	→	→	→	→
2		●		⊙		→
3	⊙	⊙				
4	⊙	○	○			●
5	⊙		→	⊙		→
6	→	⊙	→	○	●	●
7	→	●	→		●	
8	→			→		

The double circles show the successful prevention of the initiation of VT; the open circles show a decrease in the VT zone; the arrows show ineffectiveness and the filled circles show an increase in the VT zone.

Fig.2. Comparison of the preventive effects of antiarrhythmic drugs against induced ventricular tachycardia (VT).

percutaneously and positioned in the heart under fluoroscopic guidance. In the serial studies, a quadripolar or bipolar catheter, usually introduced *via* uni- or bilateral femoral veins, were positioned at the right ventricular apex, the His bundle and the high right atrium. Furthermore, the right ventricular (RV), His bundle (HBE) and high right atrial electrograms (HRA), and surface ECGs (leads I, II and V₁) were recorded. Surface

ECGs only were recorded to test the efficacy of several drugs. The femoral arterial catheter was placed in each patient to monitor the blood pressure.

Stimulation Protocol: Programmed electrical stimulation was performed with a specifically designed programmable stimulator (San-ei Sokki). The stimuli were rectangular pulses, one msec in duration and twice the diastolic thresh-

Fig.3. A typical case, in which mexiletine prevented the initiation of ventricular tachycardia (VT). This case is a 40-year-old male, without obvious cardiac disease. Ordinate: VT rate, effective refractory period (ERP) and plasma concentration of mexiletine. Abscissa: time course after intravenous administration of 150 mg of mexiletine. VT could not be induced by burst pacing from 5 to 120 min after intravenous administration. Effective refractory period of the right ventricle shortened after administration. The minimum effective plasma concentration was estimated to be 0.8 mcg/ml. VT rate in the control study was faster than that observed 210 min after administration.

Fig.4. A typical case, in which mexiletine decreased the ventricular tachycardia (VT) zone and rate of induced VT. This case is a 27-year-old male. Ordinate: VT zone and VT rate induced by a single ventricular extrastimulus. Abscissa: time course after intravenous administration. The VT zone, 300–350 msec in the control study, decreased to 300 msec 5 min after administration. VT rate decreased from 165 to 140 beats/min after administration.

Fig.5. Comparison of the effect of each antiarrhythmic drug for the ventricular tachycardia (VT) zone and VT rate initiated by ventricular extrastimuli. This case is a 27-year-old male. Ordinate: R-R interval of induced VT (V_3-V_4) showing VT rate. Abscissa: coupling time of extrastimuli (V_1-V_2), showing VT zone. The VT zone was 320 msec both in the control study and after the administration of lidocaine, disappeared after administration of disopyramide. Verapamil and propranolol increased the VT zone; the former elongated V_3-V_4 interval and the latter shortened V_3-V_4 interval.

old in amplitude. The stimulation protocol during all subsequent studies included the introduction of single and double extrastimuli during ventricular paced rhythm (S_1-S_1), incremental atrial and ventricular pacing at rates of 100 to 150 beats per minute for 15 sec and ventricular "burst" pacing, more than triple ventricular stimuli at rates of 160 to 250 beats per minute. A single premature ventricular stimulus (S_2) was introduced in late diastole during ventricular pacing at several basic cycle length from 500 to 750 msec and brought progressively closer by 10-msec decrements until ventricular refractoriness was reached. Double ventricular extrastimuli and burst pacing were used if single stimuli and ventricular rapid pacing failed to initiate the tachycardia. Double premature stimuli (S_2, S_3) were introduced starting at an S_1-S_2 interval of 50 msec longer than the ventricular effective refractory period and an S_2-S_3 equal to S_1-S_2 . S_2-S_3 was shortened until S_3 failed to capture the ventricle, and S_1-S_2 was then shortened until both S_2 reached to refractoriness. The site of stimulation was the right ventricle, but not the left ventricle.

Pharmacological Protocol: Figure 1 shows

the pharmacological protocol in our laboratory. As a general rule, antiarrhythmic drugs were discontinued for 4 to 5 drug half-lives period of time prior to the test. Following control studies, serial ones were performed after an intravenous administration of each antiarrhythmic agent. Control studies were done at each time of the acute phase before administration of the various agents. Subsequent agent was used after one to two drug half-lives of previously used one, if the inducibility, morphology and rate of induced VT were verified to be the same as those in the first control study.

Agents were intravenously administered in the following manner: 1) lidocaine 50 mg at 50 mg/min, 2) procainamide 250–1000 mg at 50 mg/min, 3) disopyramide 100 mg at 10 mg/min, 4) mexiletine 150 mg at 15 mg/min, 5) propranolol 2–4 mg at 0.5 mg/min and 6) verapamil 5–10 mg at 1 mg/min. Administration of these drugs was continued until the effect, cardiac or non-cardiac side effects occurred, or the maximum dose was achieved. Programmed electrical stimulation was performed 5 min after the termination of drug administration and at intervals of 15 min until the effect disappeared.

Fig.6. The relationship between the preventative effect and the dosage of procainamide. Ventricular tachycardia (VT), showing a rate of 180 beats/min, could be induced repeatedly by burst pacing in the control study. After 500 mg intravenous administration, VT was induced, too, but the QRS frontal axis during VT changed and VT rate decreased. After 750 mg, VT could not be initiated by burst pacing.

In some of patients plasma concentration of agents were determined, procainamide, disopyramide and lidocaine by enzyme immunoassay method, mexiletine by gas chromatography and verapamil by high performance liquid chromatography.

Evaluation Criteria of Drug Efficacy: In 8 patients, in whom sustained VT was induced by programmed electrical stimulation in the control study, we evaluated the efficacy of the drugs by the following criteria. We considered that a drug had excellent preventive effect if it prevented the initiation of the induced sustained VT after

the administration of drugs. Changes in the width of the tachycardia zone were used to judge drug efficacy; a drug was considered to be effective for prevention if it narrowed the VT zone and to be deteriorative if it increased the zone. Inducibility of the tachycardia was not used to judge efficacy. Change of the rate of the tachycardia was not used to judge efficacy. We considered that a drug was effective for the termination of the tachycardia if the induced sustained VT terminated spontaneously in 10 or less complexes after the administration of a drug.

Case	Drug		Preventive effect	
6	Group IA	Disopyramide (100mg)	effective
		Procainamide (675mg)	non-effective
5	Group IB	Mexiletine (150mg)	effective
		Lidocaine (50mg)	non-effective

Fig.7. The limitation of the electrophysiological classification of the antiarrhythmic drugs to select the effective drug. In Case 6, disopyramide prevented the initiation of ventricular tachycardia (VT), but procainamide in the same group IA was not effective. In Case 5, mexiletine prevented the induction of VT, but lidocaine in the same group IB was ineffective.

In 13 cases with repetitive ventricular response (RVR) induced by programmed electrical stimulation in the electrophysiological studies, a drug was considered to be effective only if it prevented the RVR after its administration. RVR was defined as the non-stimulated ventricular beats that occurred for one to 4 beats after a paced ventricular premature beat during ventricular pacing rhythms. In 28 patients with the attack of spontaneous sustained VT, a drug was judged to be effective for termination if it terminated the spontaneously occurring VT.

RESULTS

Induction of Sustained VT

In 8 of 11 patients with recurrent sustained VT, sustained VT could be easily and repeatedly initiated by programmed electrical stimulation. Techniques for the induction and the termination of VT in these 8 cases are listed in Table I. Sustained VT was induced by atrial pacing only

in one case, ventricular single extrastimulus in 2, ventricular double extrastimuli in one, ventricular rapid pacing in 4, and ventricular burst pacing in 3. VT was terminated by ventricular burst pacing in all cases. Table II shows the clinical features and the ECG findings in 8 patients. Except for one case of old myocardial infarction and one of aortic regurgitation, the etiology was unknown in 6 patients. The QRS morphology and frontal plane axis of the induced VT were identical to the spontaneously occurring tachycardia, and the induced VT rates were ranged within 13% of that of spontaneous rate under comparable conditions. QRS morphology of VT was right bundle branch block (RBBB) + left axis deviation (LAD) pattern in 4 cases, left bundle branch block (LBBB) pattern in 3, and RBBB + right axis deviation (RAD) pattern in one.

The prophylactic effect of more than 2 antiarrhythmic drugs on the electrode catheter induction of VT was tested in each case (Table III).

Case	Drug	Preventive effect	Terminative effect
7	Disopyramide
	Lidocaine
6	Disopyramide
	Verapamil

Fig.8. The comparison of preventative and terminative effects on induced ventricular tachycardia (VT). In Case 7, disopyramide and lidocaine terminated VT but could not prevent the initiation of VT. In Case 6, disopyramide prevented the initiation of VT, but could not terminate VT. Conversely, verapamil had only the terminative effect.

As shown in Fig. 2, procainamide was most effective for preventing the initiation of VT in 57% of cases. Disopyramide and mexiletine prevented the induction of VT in 50% and 40%, respectively. Lidocaine, propranolol and verapamil did not prevent in all cases. Verapamil was effective for prevention in the combined use with quinidine in only one case. An increase in the VT zone was found in disopyramide in 33%, propranolol in 66% and verapamil in 33%. On the other hand, a decrease in the VT zone was found in one case each with disopyramide, lidocaine and mexiletine.

Figure 3 shows a case, in which mexiletine gave excellent results in preventing the initiation of VT induced by ventricular burst pacing. This agent was effective for 2 hours after 150 mg intravenous administration, and the minimum plasma concentration that prevented the initiation of VT was 0.8 mcg/ml. In Fig. 4, another case of mexiletine is shown. Mexiletine decreased the VT zone and rate of the induced VT. The VT zone changed from 300–350 msec to 300 msec 5 min after the administration, and then gradu-

ally increased.

The effects of specific drugs were rather variable in each patient. However, in 6 of 8 patients at least one prophylactically effective drug was found. Figure 5 shows an example of the effect of each antiarrhythmic drug on the VT zone and VT rate induced by programmed electrical stimulation. Disopyramide prevented the initiation of VT, and lidocaine was not effective for the VT zone and VT rate. Both verapamil and propranolol increased the VT zone, but the former decreased VT rate and the latter increased VT rate. The complete prevention of induced VT depended on the administration dose and the plasma concentration. Figure 6 shows such a case in which the drug dose was related to the preventive effect for inducing VT. As procainamide increased step by step by each 250 mg dose at an interval of 10 min, VT rate decreased and the duration and axis of QRS wave changed at the dose of 250 mg and 500 mg, and finally no VT could be induced by any stimulation at 750 mg. The relationships between the efficacy of drug and the Vaughan

Fig. 9. The combined effect of verapamil and quinidine. This case is a 30-year-old male. Ordinate: ventricular tachycardia (VT) rate and the repetitive ventricular response (RVR) zone. Abscissa: time course after intravenous administration of verapamil. In the control study performed during an oral administration of quinidine, VT could be induced by rapid ventricular pacing and RVR was induced by a single ventricular extrastimulus. After the administration of verapamil VT could not be initiated for 90 min and RVR could not be induced for 60 min. The induced VT rate was decreased 120 min after administration.

William's drug classification³² by electrophysiological properties were analyzed. The effects of procainamide and disopyramide, belonging to group IA, were the same in 3 of 5 cases, but different in 2 cases. The effects of mexiletine and lidocaine, belonging to group IB, were the same in one case, but different in 2 cases (Fig. 7). The preventive effect and the terminative effect on induced VT for the same drug were compared. In one case, as shown in Fig. 8, disopyramide, and lidocaine were ineffective for prevention of VT, but were effective for the termination of VT. In another case, disopyramide was only effective for prevention and verapamil was only effective for termination. In 2 patients, the combination effects of regimens using 2 antiarrhythmic drugs were evaluated after the failure of each agent to prevent the initiation of VT. Figure 9 shows one case, in which a single administration of 0.6 g/day of quinidine was not effective, while verapamil prevented the induction of VT for 90 min after the administration. Figure 10 shows another case. Only

disopyramide had a preventive effect and only verapamil had a terminative effect, but the combination of these regimens had neither the preventive nor the terminative effect.

Induction of RVR

RVR to a single ventricular extrastimulus during ventricular pacing was observed in 13 patients: 3 with recurrent sustained VT and 10 with non-sustained VT. These RVRs were morphologically identical to the spontaneously occurring tachycardia in only 3 of the 13 patients (Table IV). The preventive effect of various antiarrhythmic drugs against electrode catheter-induced RVRs was studied. Disopyramide was most effective for prevention of RVR in 75%, but procainamide, belonging to the same group IA, was only effective in 33%. Lidocaine and verapamil were effective in one half of these cases. Propranolol was deteriorative in 2 cases (Fig. 11). Figure 12 shows an example of these cases, in which RVR induced by programmed electrical stimulation was morphologically dif-

Fig.10. The combined effect of verapamil and disopyramide. This is a 27-year-old male. Ordinate: R-R interval of induced VT, (V_3-V_4). Abscissa: coupling time of extrastimuli, VT zone (V_1-V_2). The combination of verapamil, having a terminative effect and disopyramide having a preventative effect, showed neither the terminative effect nor the preventative effect. As compared to the control study, V_1-V_2 interval and V_3-V_4 interval increased after an administration of verapamil. Furthermore, V_3-V_4 interval increased with the addition of disopyramide.

ferent from the spontaneously occurring arrhythmia. Lidocaine was successful for preventing RVR, but was ineffective for preventing the spontaneous non-sustained VT.

Spontaneous Sustained VT

Terminative effect of individual agents on spontaneous sustained VT was evaluated in 28 patients (Table V). The drugs in group IA were

Fig.11. Comparison of the preventive effects of antiarrhythmic drugs against repetitive ventricular response (RVR).

TABLE IV PREVENTIVE EFFECT OF SEVERAL ANTIARRHYTHMIC DRUGS AGAINST RVR INDUCED BY PROGRAMMED ELECTRICAL STIMULATION IN THIRTEEN PATIENTS

Case	QRS of RVR & spon. VT	Group IA		Group IB		Group II	Group IV
		Procainamide	Disopyramide	Lidocaine	Mexiletine	Propranolol	Verapamil
1	S		●			●	○
2	S		○				○
3	S		○		○	●	○
	D		→		→	→	○
4	D	●					
5	D			→			●
6	D						○
7	D	○		○			→
8	D			○			→
9	D	→		●			→
10	D		○				
11	D			→			
12	D		○				
13	D			○			

The open circles show the successful prevention of RVR; the arrows show ineffectiveness and the filled circles show deteriorative effects. S indicates that QRS of RVR and spontaneous VT are the same; D indicates that they are different. RVR = repetitive ventricular response

Fig.12. A typical case, in which lidocaine prevented repetitive ventricular response (RVR). This case is a 50-year-old female. Ordinate: the incidence of RVR in the same condition of programmed electrical stimulation. Abscissa: time course after intravenous administration of 50 mg of lidocaine. The QRS of RVR was not identical to that of spontaneously occurring ventricular tachycardia (VT). RVR could not be induced for 22 min after lidocaine administration.

more effective than those in other groups. Disopyramide was effective in 80% and procainamide in 62%. Lidocaine terminated sustained VT in

33%, but induced ventricular fibrillation in one case. Both propranolol and verapamil were effective in one case each (Fig. 13).

TABLE V TERMINATIVE EFFECT OF SEVERAL ANTIARRHYTHMIC DRUGS AGAINST SPONTANEOUSLY OCCURRING SUSTAINED VT IN TWENTY-EIGHT PATIENTS

Case	Age	Sex	Basic disease	Group IA		Group IB	Group II	Group IV
				Procainamide	Disopyramide	Lidocaine	Propranolol	Verapamil
1	26	f		→	→	●		
2	23	f	ICM	○	○	→		
3	32	m		○		→		
4	27	m	ICM	→		→		
5	63	m	OMI	○		○	○	
6	60	m	OMI			→		
7	63	f	AMI	○		○		
8	56	m				→		
9	58	m		○	○	→	→	→
10	13	f		→	○	→	→	
11	29	m	ICM	○	○	→		
12	32	f	ICM		○		→	
13	40	m		→				
14	40	m		○	○			
15	71	m	III° AV block → PM		○	→		
16	13	m		○		→	→	
17	21	m		→		→	→	
18	67	m	OMI	○				
19	44	m		○		○		
20	16	f	ICM	○	○	○		→
21	67	f	angina pectoris			○		
22	24	m		○				
23	26	m		→		→		
24	30	m		→	→	→	→	○
25	45	m	OMI			○		
26	35	m		○				
27	27	m		→				
28	40	m				○		

The open circles show the termination of sustained ventricular tachycardia (VT); the arrows show ineffectiveness and the filled circles show the induction of ventricular fibrillation.

ICM = idiopathic cardiomyopathy, OMI = old myocardial infarction, AMI = acute myocardial infarction, PM = pacemaker implantation, m = male, f = female

DISCUSSION

Evaluation of Electrophysiological Testing of VT

The therapy of recurrent sustained VT is often unsuccessful and drugs and their dose have been empirically selected, usually based on trial and error in spontaneous episodes of VT. It has been attempted to predict effectiveness of antiarrhythmic drugs on VT from pharmacological suppression of spontaneous isolated VPBs. Recently trendsetting using continuous ECG

monitoring after sequential administration of a variety of antiarrhythmic drugs has been utilized for an assessment of drug efficacy against VPBs.^{3,26} In many patients, this method is considerably effective when attacks of VT recur frequently or when there is a clear relationship between numbers or grades of VPBs and the initiation of VT. However, this method has some limitations. Some patients with recurrent sustained VT rarely have VPB between episodes of VT. Some patients, whose VPBs were almost com-

Fig.13. Comparison of terminative effect of various antiarrhythmic drugs against spontaneously occurring sustained ventricular tachycardia. Vf = ventricular fibrillation

pletely suppressed by antiarrhythmic drugs, still have episodes of VT, and some patients, in whom recurrences of VT were successfully prevented by a particular drug, have persistently complex VPBs.

In 1972, Wellens et al.^{28,29} have reported that the arrhythmia in patients with chronic recurrent VT can be initiated repeatedly by programmed electrical stimulation. Thereafter, using these stimulation technique, the mechanism of VT in human heart has been able to be studied directly, and much attention has been paid to the serial electrophysiological testing in the assessment of the drug efficacy for sustained VT.¹²⁻²⁵

In 80–95% patients with clinically documented VT, the same arrhythmia can be induced repeatedly by programmed electrical stimulation.^{6,13,15,17,28,30} In cases without previous tachycardia or syncope,^{15,17,22,30} VT is rarely induced by electrophysiological stresses. In our present study, sustained VT could be initiated repeatedly in 8 of 11 patients with recurrent sustained VT by pacer technique. One of the reasons why VT could not be induced in 3 cases may be that left ventricular pacing was not attempted in our study. In 10% of the patients with inducible VT, VT can be initiated only by a stimulation of the left ventricle.²⁶

The use of an electrophysiological protocol for the selection of drug therapy is based on the assumption that VT induced by pacer technique is identical to the spontaneous VT.^{12,13,15,19-22,24-26,31} In our 8 patients, the induced VT was morphologically identical to the spontane-

ously occurring VT, and the induced VT rates were ranged within 13% of that of the spontaneous rates. Similar results have been reported by other authors.^{15,30} It has been reported that the induced VT is morphologically different from the spontaneous VT in 5–20% of patients.^{6,13,15,20,30} The clinical significance of this non-clinical VT has not been established, but this non-clinical VT could not be found in our present observations.

In 64–80% of patients in whom VT was induced repeatedly, VT usually can be terminated by programmed electrical stimulation.^{5,6,10,13,15,20,22} We were able to terminate VT by burst pacing in all cases. It has been reported that the rate of VT accelerated in 1–10% of patients following burst pacing.^{6,10,13} Therefore, precautions must be taken in applying this technique to some patients.

Evaluation of Pharmacological Testing of VT

Pharmacological protocol is not well established. Our protocol also has the following problems: 1) In our study, the maximum dose of procainamide was 1,000 mg, disopyramide 100 mg, lidocaine 50 mg, mexiletine 150 mg, propranolol 4 mg and verapamil 10 mg. In Horowitz's protocol,^{12,26} however, the dose of procainamide is 2,500 mg, lidocaine 300 mg and propranolol 0.2 mg/kg. 2) As a general rule, the interval between one drug and another requires at least 4 drug half-lives, but we could not always follow up, because the total testing period was limited. Therefore, we cannot completely ex-

clude the possible vestigial effect of previously administered agents. 3) We could not precisely evaluate the efficacy of orally administered drug, since minimum effective plasma concentration of a drug is not always the same when it is administered orally and intravenously.

Evaluation method of drug efficacy in the serial electrophysiological testing has not been established. A drug should be considered to be effective only when it is able to prevent the initiation of sustained VT after its administration. This is thought to be the only reliable index for the long-term suppression of VT²⁶ In our study, as well as Fisher's report,¹⁵ changes in the width of the tachycardia zone were used in order to judge drug efficacy. It is probably effective for the prevention of induced VT when the VT zone decreases, and deleterious when it increases. This effect may be considered to be predictive for the long-term efficacy in the prevention of VT. The antiarrhythmic drugs may also alter the inducibility of VT and its rate. As Horowitz has reported, changes neither in the inducibility of VT nor in its rate may predict the frequency of subsequent episodes of spontaneous VT, and thus, may not be used as a measure of efficacy^{12,26} We also ignored changes in the inducibility of VT and its rate using these drugs. Further studies should be done to establish the evaluation criteria for drug efficacy in the future.

Drug Efficacy for Induced VT

Recently attempts have been made to classify the antiarrhythmic drug based on their electrophysiological properties^{32,33}: membrane depressant, action potential duration, sympatholytic, inward calcium current block and others. The electrophysiological classification of Vaughan Williams is most widely accepted³³ According to the classification, we used procainamide and disopyramide in group IA, lidocaine and mexiletine in group IB, propranolol in group II and verapamil in group IV.

In our study, procainamide, disopyramide and mexiletine were most effective in preventing the initiation of VT. However, the effects of each of these drugs were different from patient to patient and were unpredictable. No reliable clinical or electrophysiological parameters have been found for predicting the effects of each drug on VT.

By electrophysiological-pharmacological testing in other institutions, the drugs in group IA were most effective in preventing the initia-

tion of VT and the effective rate was between 30 and 50%.^{12,16,20,26} We also found similar results. Procainamide is most effective in group IA. Although its effective rate was 45% according to Horowitz et al.¹² and 33% according to Wellens et al.¹⁶ the effective rate of procainamide in our study was 57%, being higher than that in other reports in spite of the use of smaller doses. Disopyramide, a recently developed drug, was effective next to procainamide and its effective rate was 50%. According to Horowitz et al.¹² this agent prevents the initiation of VT in only 20% of total cases. The reason for these differences is likely to be due to the difference in the basic cardiac disease. In another study, approximately 90% patients had organic heart diseases, especially coronary artery disease.²⁵ It should be kept in mind that disopyramide widened VT zone. Since the initiation of VT depends on the critical relationship between conduction velocity and refractoriness, an alteration of this relationship could not only suppress, but also facilitate the initiation of VT. Therefore, the procainamide, as well as disopyramide, may also increase the VT zone. Drugs in the same group IA were not always interchangeable. In our 2 patients in whom a group IA agent prevented VT, the arrhythmia could not be prevented by the other agents in the same group. The reasons of this difference are not apparent, but from a clinical point of view it must be stressed that the electrophysiological classification has a limitation.

The suppression of VT during electrophysiological testing is usually observed at sufficiently high plasma concentrations of drugs.²⁶ In our study, 2 patients required plasma concentration of procainamide higher than 8 mg/L, which is the usual effective plasma concentration for VPBs. Therefore, electrophysiological testing is useful to select an effective antiarrhythmic drug and also to determine effective dose of that drug. Lidocaine in group IB has been reported to be less frequently effective in preventing the initiation of VT and the effective rate of this agent ranges from 5 to 20%.^{12,13,15,26} In our study, however, lidocaine was not effective in any patient. Differences in the dosage of lidocaine and the basic diseases may cause different results. Mexiletine, a recently developed drug in the same group as lidocaine, was effective in 50% of cases. Dimarco et al.³⁴ have also reported that mexiletine prevented the initiation of VT in 13 of 35 patients. Lidocaine and mexiletine occasionally

accelerate the rate of induced VT without any preventive effect.¹² This seems reasonable, since these agents increase the conduction velocity and/or shortening of ventricular refractoriness in the re-entrant circuit. In our 2 patients, however, mexiletine decreased VT rate. Recently El-Sherif et al³⁵ have reported that lidocaine depressed conduction velocity in ischemic tissue of intact experimental animals.

Propranolol, β -blocker, was not effective in our 3 patients, even caused a deterioration in 2 cases. Generally propranolol has been effective for the prevention of VT in patients with exercise-induced VT.^{12,16} In this group, VT is initiated by programmed electrical stimulation after the administration of isoproterenol.^{15,31} These patients were not included in our study.

Verapamil, Ca-antagonist, has been thought to be less effective in preventing the initiation of VT.¹⁶ In our study, verapamil alone was not effective in preventing the initiation of VT. It is interesting that this agent prevented the initiation of VT in combination with quinidine, which was ineffective in preventing the initiation of VT in one of our patients. Also in 2 of our patients, verapamil increased the VT zone, decreased VT rate and terminated spontaneously the induced VT. Belhassen et al³⁶ have reported one case, whose VT responded to verapamil. Cranefield³⁷ stressed the role of the calcium-dependent slow inward current in the genesis of arrhythmias. Since verapamil suppresses the slow inward current, two mechanisms have been suggested.³⁸ One possible mechanism is that slow-response action potential is involved in the re-entrant circuit and another one is an appearance of automaticity triggered as a result of delayed after-potential, which is known to be slow-channel dependent.³⁹

In 2 of our patients, the ability to terminate the induced VT did not necessarily correlate with the ability to prevent its initiation. This result is identical to that of Wellens.¹⁶ Although lidocaine terminated the spontaneously occurring VT in 33% patients, this agent was not effective in preventing the initiation of VT by electrical stimulation. This result may be due to the differences in drug dosage required for the prevention and the termination of VT and in the mechanism of the initiation and the maintenance of VT. In clinical practice, this result should be kept in mind.

Fisher et al⁶ have found that combination regimens were not only effective but also neces-

sary to control VT in more than one half of their patients. On the other hand, Horowitz et al²⁶ have not found that combinations of 2 and 3 drugs were effective when all single agents failed to prevent the initiation of VT at their maximally tolerated levels. In one of our patients, the combination of quinidine and verapamil was effective in preventing the initiation of VT. In one case, combined use of disopyramide, which prevented VT, and verapamil, which terminated VT, was not effective for the prevention and the termination of VT. It is generally thought that combination regimens of different groups, for example, procainamide and propranolol, are effective. However, the effect of combination regimens using more than 2 antiarrhythmic drugs is controversial and unpredictable. Therefore, this provocative testing is useful for the assessment of the efficacy of combination therapy.

Evaluation of Drug Efficacy for RVR

A definition of RVR has not been established. We used RVR following Akhtar's definition.⁴⁰ However, according to Ruskin et al,^{2,3} RVR is designated as the 3 or more beats of ventricular origin which occurred in response to a single programmed stimulation. The clinical significance of the RVR has gained considerable interest.⁴⁰⁻⁴⁵ There are 2 types of RVR, i.e., bundle branch reentry and intraventricular reentry (IVR). Greene's study^{42,43} suggested that RVR due to IVR has a predictive value for the development of VT or sudden death. Conversely, Mason's study⁴⁴ could not substantiate these results. Therefore, the predictive value of IVR is controversial at present and not sufficiently proven to be useful for clinical practice. In 10 of 13 patients, QRS configuration of RVR was not similar to the arrhythmia occurring clinically. Reproducibility and sensitivity of RVR are also problems in this test. Therefore, the value of the pharmacological suppression of RVR as an index for the prevention against life-threatening ventricular arrhythmias and sudden death remains to be controversial and unconfirmed.

Indication of Provocative Testing

The benefit of provocative studies, in addition to the above-mentioned medical factors, is a shortening of the hospitalization period and a reduction of the economic cost. On the other hand, the risk of provocative testing, including ventricular fibrillation, hemodynamic deteriora-

tion, mental and physical stress and anxiety, must be recognized. Therefore, the indication of provocative studies should be decided with careful consideration for its risks/benefits. It is very important to clarify the criteria for the indication of this method in each institution. At present, our tentative indication of electrophysiological-pharmacological testing is as follows: 1) Recurrent sustained VT, especially refractory VT. 2) The benefits/risks of provocative testing must be explained to both the patient and the family, and an informed consent must be obtained. 3) The team of cardiologists with sufficient knowledge of arrhythmias and skillfulness in handling cardiac emergency, and adequate equipment for defibrillation and others must be available. 4) Before provocative testing complete examinations must be done non-invasively and invasively to obtain reliable data about the basic cardiac disease and the cardiac function. Furthermore, age and daily activity should be considered. The indication of this method for the treatment of other ventricular arrhythmias, such as non-sustained VT,³⁰ ventricular fibrillation⁴⁶ and VT induced by exercise, and for the identification of the patients, who have a risk of syncope and sudden death,⁴² has not been clarified and is still rudimentary.

We consider that, in patients with sustained VT, the electrophysiological-pharmacological testing can accurately predict the effectiveness of a particular regimen and combination regimens, and can identify the deleterious effects of certain drugs in acute phase. Although our cases studied were small in number and not followed up, it could be concluded that this method could be clinically useful if patients were carefully selected and all testings were performed cautiously. Recently some authors have reported that this arrhythmia-induction technique predicted accurately the clinical effectiveness of drugs used in a long-term treatment of recurrent VT.²⁴⁻²⁶ However, before we can advocate this method universally, further experience, especially long-term follow-up, is required, and possible applications and limitations of this technique should be studied in detail.

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