difference between the cycle length of VT and the VT-interrupting critical paced cycle length in an electrophysiologic (EP) study when VT was entrained with rapid pacing. Rapid pacing was repeated at progressively shorter cycle lengths until VT was interrupted[13-15]. The efficacy of the class I antiarrhythmic drugs was only predictable by seeing the response of the zone of entrainment. When VT induction was prevented by a drug, a significant narrowing of the zone of entrainment was observed at the intermediate doses of the drug. After an addition of the same drug to the final dosage, VT became uninducible[14,15].

As an extension of the study, we assessed the efficacy of dl-sotalol in relation to the basal electrophysiological characteristics of VT, namely, the cycle length and the zone of entrainment.

PATIENTS AND METHODS

Patients

Twenty-two consecutive patients with reentrant VT underwent an electrophysiologic study. The clinical characteristics of the patients are shown in Table 1. Criteria for inclusion was that VT was inducible in the control state and interrupted with rapid ventricular pacing at a critical paced cycle length[4,13-15]. During the rapid pacing, VT was confirmed to be transiently entrained with rapid ventricular pacing[16,17].

Table 1. Clinical profiles of patients

Age (years)	56±15 years (16-71)
	Male/Female=15/6
Underlying heart diseases	
OMI	13
DCM	3
ARVD	2
LV aneurysm*	1
Sarcoidosis	1
None	1

*, left ventricular aneurysm unrelated to coronary artery disease.

Electrophysiologic study

An electrophysiologic study was performed in a drug-free state after obtaining informed consent in a non-sedated and postabsorptive state[4,13-15]. Two to three quadripolar electrode catheters with an interelectrode distance of 5 mm (6 Fr. Multipurpose catheters, USCI, Boston, MA, USA) were inserted via the right femoral vein and placed against the high right atrium, across the tricuspid valve, and at the apex of the right ventricle. Another electrode catheter was placed in the left ventricle via the right femoral artery and placed at the site of the earliest activation during VT.

Bipolar intracavitary electrograms were filtered at 30 and 500 Hz and recorded on a strip chart at a paper speed of 100 mm/sec or 200 mm/sec (Mingograf 7, Siemens-Elma, Solna, Sweden). Surface leads I, II and V1 were recorded simultaneously with intracavitary electrograms. All data were stored on magnetic tape (Cassette Recorder, TEAC Co., Tokyo, Japan) and retrieved later for use on a thermal recorder (Thermal Recorder, Fukuda Denshi Co., Tokyo, Japan).

Induction of VT

Stimulation was attempted using the pair of the distal and third electrodes, and the induction of VT was first attempted at the apex of the right ventricle using 1-3 extrastimuli at two basic cycle lengths of 600 msec and 400 msec. Rapid pacing was attempted at cycle lengths between 600 and 286 msec. When VT was not induced from the apex, programmed stimulation was applied at the outflow tract of the right ventricle. Finally, the induction of VT was attempted from the left ventricle for those in whom VT was not inducible from the right ventricle. Induced VT was recorded on a 12-lead electrocardiogram and used for the analysis of VT morphology.

Entrainment and interruption of VT

Rapid pacing was attempted either at the apex or the outflow tract of the right ventricle. In the second study, the pacing site was chosen as close as possible to that of the baseline study. We used the following criteria of transient entrainment: 1) constant fusion during rapid pacing except for the last non-fused but captured beat which occurred at the paced cycle length in the surface electrocardiogram or in the electrogram at the exit from the area of slow conduction[4,13-16]; 2) a constant but different degree of fusion at differing pacing rates[16,17]; 3) advancement of the local electrogram at the exit without any change in the morphology[4,13-15].

Rapid pacing was continued for 5-10 sec starting at a cycle length which was 10-20 msec shorter than the cycle length of VT. It was repeated at a progressively shorter cycle length after a decrement in steps of 10

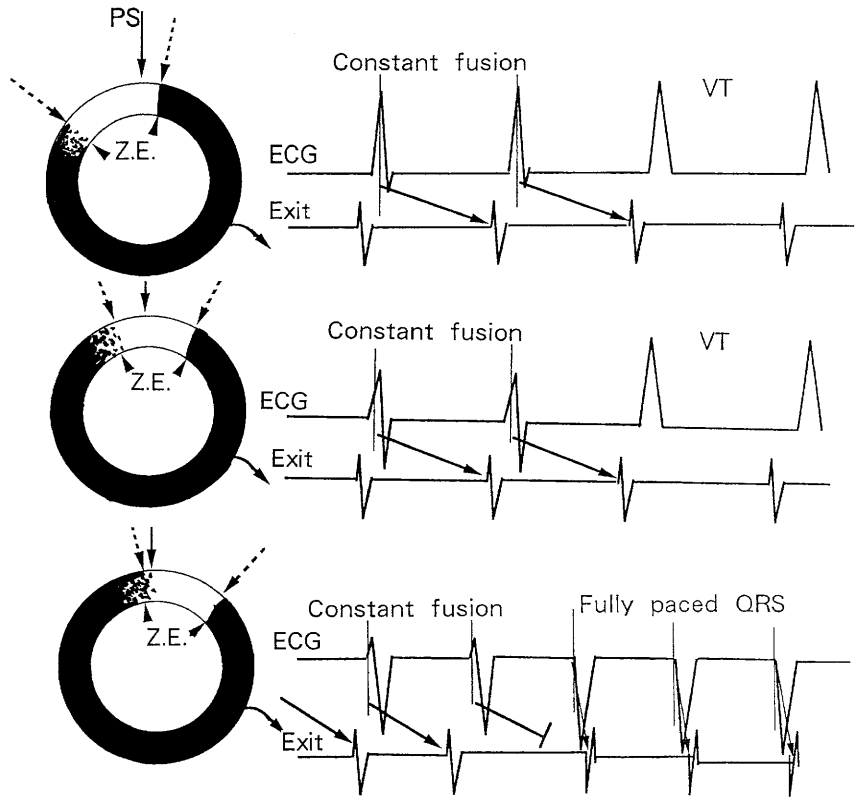

Fig. 1. Interruption of ventricular tachycardia with rapid pacing at the block cycle length.

The cycle length of VT was prolonged from 260 msec in the control state to 360 msec during therapy with dl-sotalol (320 mg/day), and interrupted at the block cycle length of 320 msec. The surface QRS complexes showed almost an identical morphology to that of the fully paced ones (not shown), but the intracavitary electrogram was identical to the paced cycle length and entrained orthodromically until it showed a sudden change in the morphology and the timing of activation, a finding consistent with the orthodromic block which was observed frequently as reported earlier[4,9,10]. Following such an abrupt change in the local electrogram, VT was always interrupted, as was evident after the cessation of rapid pacing.

The width of the zone of entrainment of this patient was 40 msec while it was 60 msec before the administration of the drug.

msec. When VT was interrupted at a critically paced cycle length, this longest VT-interrupting paced cycle length was acknowledged as the block cycle length. During pacing at the block cycle length, the localized block was confirmed as reported earlier (Fig. 1) and the initial fused QRS complexes were replaced abruptly by fully-paced QRS ones; the local electrogram at the exit from the zone of slow conduction showed an abrupt change in morphology and timing of activation as reported elsewhere[4,13-15].

Drug-administration

DL-sotalol was administered initially at 160 mg/day for 7 days and increased to 240-320 mg. The drug testing was performed 2-3 weeks after the administration of dl-sotalol.

Definitions

Sustained VT was defined as VT which lasted for 30 sec or longer and non-sustained VT was that lasting more than 3 beats but terminated within 30 sec.

The drug was considered effective if sustained VT was not induced after completion of the whole stimulation protocol after the administration of dl-sotalol.

The width of the excitable gap was estimated from the zone of entrainment which was defined as the

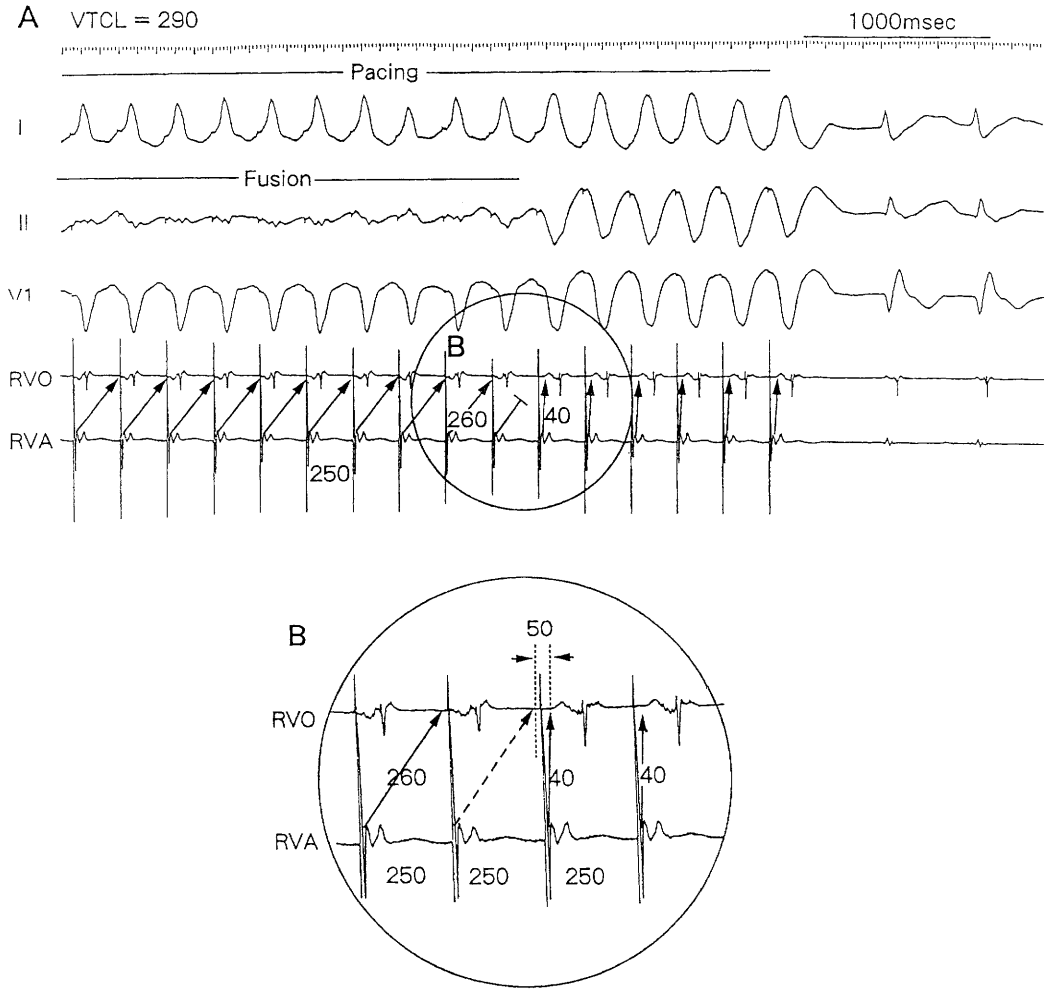

Fig. 2. Changes in the effective refractory period in responders and non-responders.
The prolongation was significant in the responder group (R) both at 600 msec and 400 msec of the basic cycle length, respectively ($P<0.001$). The basal values did not different between the two groups. The changes were greater in the responders than the non-responders (NR) but not significantly ($0.05<P<0.1$). ERP, effective refractory period.

difference between the cycle length of VT and the block cycle length.

The effective refractory period was determined at the apex of the right ventricle at the basic cycle length of 600 msec and 400 msec as the longest coupling interval of premature stimuli which failed to capture the myocardium.

Data analysis

The patients were divided into two groups according to the results of the drug testing and the cycle length of VT, and the zones of entrainment at the control study were compared between the responders and the non-responders. The changes in the QT interval and the effective refractory period were also compared between the two groups.

The values are presented as mean $\pm$SD. When appropriate, paired or un-paired t-tests were used for comparisons and a P-value <0.05 was considered to be significant.

RESULTS

Induction and transient entrainment of VT

From the entry criterion, a sustained monomorphic VT with the mean cycle length of 288 ± 56 msec was

Table 2. Comparisons of clinical profiles and electrophysiological parameters

	Responders (n=11)	Non-responders (n=10)
Body length (cm)	162±9	158±8
Body weight (Kg)	58±12	57±11
Dose (mg/day)	276±61	296±39
VTCL (msec)	300±72	275±21
Excitable gap (msec)	57±27	50±16

VTCL, the cycle length of ventricular tachycardia.

Table 3. Comparisons of the basal electrophysiologic parameters

UDH	VTCL	BCL	EZ	ERP (control/drug)
Responders				
OMI	240	210	30	250/290
OMI	230	190	40	250/280
OMI	250	200	50	240/280
OMI	420	350	70	230/320
OMI	360	260	100	250/300
OMI	290	200	90	250/290
ARVD	250	200	50	270/320
ARVD	350	300	50	270/270
T/F	240	200	40	250/270
SARC	410	380	30	240/270
NONE	260	210	50	250/290
	300±72	246±68	57±27	250±12/289±18
Non-responders				
OMI	280	250	30	240/290
OMI	280	230	50	230/280
OMI	280	220	60	220/260
OMI	230	200	30	250/250
OMI	280	220	60	250/270
OMI	290	250	40	230/290
DCM	270	190	80	290/300
DCM	310	260	50	270/290
DCM	260	200	60	240/240
LVA	270	230	40	240/290
	275±21	225±24	50±16	246±21/276±20

induced and VT was terminated at the block cycle length of 241±65 msec with rapid ventricular pacing (Fig. 2). During rapid pacing, constant fusion was confirmed at relatively longer paced cycle lengths and at shorter cycle lengths. Progressive fusion was confirmed in all patients.

Drug-efficacy

After the administration of dl-sotalol, the RR interval was prolonged from 884±95 ms to 1077±130 ms ($P<0.01$) and the QT interval was prolonged from 421±30 ms to 483±50 ms ($P<0.01$). The effective refractory period was prolonged from 245±17 ms to 278±27 ms ($P<0.01$). The drug was able to prevent VT induction in 11 of 22 patients (responders) and in the remaining

11 patients (non-responders), monomorphic VT was induced during sotalol tehrapy.

In the non-responders, the cycle length of the induced VT was prolonged from 275±21 to 336±47 ms ($P<0.01$). The block cycle length was also prolonged but insignificantly from 225±24 ms to 274±62 ms ($P>0.1$). Consequently, the width of the excitable gap was unchanged: 50±16 vs. 63±32 ms ($P>0.2$).

Comparisons of the baseline characteristics of VT

As summarized in Table 2, there was no significant difference in the dosage of the drug as well as the body length or body weight. The cycle length of VT or the width of the excitable gap was not different between the responders and the non-responders: 300±72 vs. 275±21 and 57±27 vs. 50±16 msec, respcetively (Table 3). The effective refractory period was prolonged after dl-sotalol in the two groups: from 250±12 to 285±15 in the responders and from 240±21 to 267±41 msec in the non-responders, respectively (Table 3).

DISCUSSION

Monomorphic sustained VT which is inducible with programmed stimulation has been considered to be due to reentry, and electrophysiological findings consistent with a reentrant mechanism have been accumulated: the phenomenon of transient entrainment[16,17], diastolic or continuous electrical activity in a circumscribed area[18], the ability to pace the reentry pathway[19,20,21], or proof of the revolution of the wave fronts[22,23,24]. Such electrophysiological findings can be obtained not only in VT associated with prior myocardial infarction but also in monomorphic VT unrelated to coronary artery diseases as we reported[4,10]. The ability to reset or entrain VT by extrastimuli or rapid pacing means that VT has an excitable gap which can be a target in the therapy of reentrant VT[25].

When antiarrhythmic agents were tested, the ability to prevent the induction of sustained VT was confirmed at a rate of 50% or less during the serial testing[5-7]. dl-sotalol is a class III agent having β-adrenergic blocking action and the drug-efficacy has been shown to be superior to other class I agents[9,26]; in a study with the largest number of patients, inducible VT was suppressed in 94 of 269 patients (35%)[27]. Other smaller studies showed the suppression of inducible VT in 23-45%[28-30]. In the present study, VT become uninducible in 11 (52%) of 21 patients.

When VT/VF is suppressed by sotalol, sotalol treatment led to a marked reduction in arrhythmic events[12,27,28,31,32].

Prediction of drug efficacy

To date, previous studies have proposed some parameters as predictors of the efficacy of class I agents. These include responses to drugs of the effective refractory period, HV interval, intraventricular conduction, or changes in the width of the paced QRS complexes[33-38]. When dl-sotalol was tested, a prolongation of the effective refractory period (>300 msec) was associated with the drug-efficacy[27] or a decrease in the late potential of the signal averaged ECG[39]. However, other workers denied these findings and reported that neither a change in ECG nor electrophysiological parameters including the effective refractory period was associated with the ability to suppress the induction of VT[29].

Recently, we determined the block cycle length as the VT-interrupting longest cycle length, and the zone of entrainment was obtained as the difference between the VT cycle length and the block cycle length[13,14]. During pacing at the block cycle length, a 1 : 1 conduction (orthodromic block) was assumed to fall within the zone of slow conduction. Following the orthodromic block, the exit was captured directly by the paced wave fronts resulting in fully paced QRS complexes. The width of the zone of entrainment was assumed to represent the width of the excitable gap, and when class I drugs were tested, a significant narrowing at the intermediate dosage of antiarrhythmic drug was associated with the prevention of a VT induction at the final dosage of the drug[13,14].

As a possible mechanism for the prevention of VT induction, the prolongation of the block cycle to reach (or exceed) the VT cycle length would interfere too much for the wave fronts to revolve: reentry within the slow conduction zone would be impossible. Since the block cycle length was always much longer than the effective refractory though the latter was measured not within the reentrant circuit but in normal tissue, something other than an effective refractory period must be engaged. The post-repolarization refractoriness would be a candidate which results in 1 : 1 conduction failure.

In summary, the response of the block cycle length to the drug was not determined at the intermediate dosage. The efficacy was not predictable from the basal characteristics of VT including the block cycle length and the zone of entrainment.

Limitations

One limitation of this study is the small number of patients and the diversity of the underlying heart diseases. However, the mechanism of VT must be reentry as the phenomenon of transient entrainment was demonstrated in all patients. During pacing at the VT-interrupting critical paced cycle length, the precise site of the orthodromic block or its mechanism was not shown, but this would be difficult in a clinical study. The precise relation between the width of the zone of entrainment and that of the excitable gap remains to be determined.

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