Drug-induced narrowing of the width of the zone of entrainment as a predictor of the subsequent non-inducibility of reentrant ventricular tachycardia after an additional dose of an antiarrhythmic drug

Yoshifusa Aizawa, Masaomi Chinushi, Naoki Naitoh, Akira Shibata

Abstract

Background—The efficacy of drugs used to treat inducible monomorphic sustained ventricular tachycardia (VT) has been assessed by investigating their ability to suppress inducibility, but the mechanism of the drug action remains to be determined.

Objectives—To determine electrophysiological variables that predict inducibility, divided doses of class I antiarrhythmic drugs were given and their effects were analysed, particularly the ability of the final dose to suppress inducibility.

Methods—The excitable gap was estimated by the zone of entrainment, which was defined as the difference between the cycle length of VT and the longest paced cycle length that interrupted VT during entrainment of VT with rapid pacing at paced cycle lengths in decrements of 10 ms. The cycle length of VT, the block cycle length, and the zone of entrainment were measured in the drug-free state and after intermediate and final doses of procainamide, disopyramide, cibenzoline, and mexiletine.

Results—Sustained monomorphic VT with a mean (SD) cycle length of 285 (43) ms was induced in 8 patients. It was entrained and interrupted at the block cycle length of 231 (31) ms. The width of the zone of entrainment was 54 (23) ms. In 8 studies VT was not inducible at final doses of procainamide in 4, cibenzoline in 1, and mexiletine in 3. In another 10 studies (procainamide in 4, disopyramide in 1, cibenzoline in 2, and mexiletine in 3), VT remained inducible at the intermediate dose and at the final dose. The cycle length of VT was prolonged to a similar degree in studies of effective and ineffective drugs, but the cycle length that blocked VT was longer at the intermediate dose of the effective drugs. Consequently, the width of the zone of entrainment was significantly narrowed at the intermediate dose of effective drugs and the width of the zone of entrainment was narrower than when ineffective drugs were given (22 (13) ms vs 76 (18) or 75 (37) ms at the intermediate and final doses respectively (P < 0.02).

Conclusion—Drugs that narrowed the zone of entrainment were associated with non-inducibility of VT after the final dose of the drug was given. The baseline variables did not predict the responses to class I antiarrhythmic drugs.

(Heart 1996;75:165-170)

Keywords: ventricular tachycardia; zone of entrainment; class I antiarrhythmic drug

Most monomorphic sustained ventricular tachycardia (VT) in humans is believed to be caused by reentry, as suggested by the transient entrainment,^1^ 2 and the demonstration of the zone of slow conduction. The conductive properties of the reentry circuit have been reported.4-6

When VT is inducible, drug efficacy is assessed by electrophysiological studies,7-8 and antiarrhythmic drugs that suppress the inducibility of VT are regarded as effective. However, the mechanism of the drug-induced non-inducibility is unknown.

We sought possible predictors of drug efficacy among the characteristics of VT—particularly the paced cycle length that interrupted VT and the width of the zone of entrainment.9 10

The paced cycle that interrupted VT was defined as the longest paced cycle length that interrupted VT during rapid pacing in which the cycle length was reduced progressively in steps of 10 ms.9 10

Patients and methods

PATIENT SELECTION

In eight consecutive patients the efficacy of class I antiarrhythmic drugs11 was assessed by electrophysiological study using divided doses. Each patient fulfilled the following criteria: (a) VT was entrained with rapid pacing at progressively shorter cycle lengths until VT was interrupted at a critical cycle length in the drug-free state; (b) the VT induced after the administration of antiarrhythmic drugs had a configuration that was identical to that of the drug-free VT and VT was interrupted with rapid pacing; (c) the efficacy of each drug was assessed at two doses.
We studied eight patients (one woman) aged 20–76 (mean 57 (14)). VT was related to old myocardial infarction in four patients in whom an occluded coronary artery was shown by angiography and in whom the ejection fraction measured by left ventriculography was 0.43 (0.15). One patient had idiopathic dilated cardiomyopathy and an ejection fraction of 0.40. One patient had had an operation for double outlet of the right ventricle and one patient had arrhythmogenic right ventricular dysplasia.12 No structural heart disease was detectable in the remaining patient. These three patients had angiographically normal coronary arteries and an ejection fraction of > 0.40.

ELECTROPHYSIOLOGICAL STUDY
After the patients gave written consent, an electrophysiological study was performed in the standard manner13,14 and as described elsewhere.13-15 The protocol for induction of VT consisted of single and double (triple when necessary) extrastimuli given after eight basic stimuli at two cycle lengths, 600 ms and 400 ms, and incremental pacing at cycle lengths of 600–286 ms for 5–15 seconds.

Stimulation was performed from two sites in the right ventricle and a single site in the left ventricle. When VT was not induced, isoprenaline was infused intravenously to keep the sinus rate 20% above the drug free level and programmed stimulation was repeated.

Every episode of induced VT was recorded on 12 lead electrocardiogram and the activation sequence was mapped to localise the earliest site of activation.15 The site was regarded as the exit from the zone of slow conduction.

ENTRAINMENT OF VT
After induction of VT, rapid pacing was performed as reported previously,13,14,16 starting at a cycle length 10–20 ms shorter than that of VT, and repeated with decrements of 10 ms until VT was terminated. Rapid pacing was continued for 5–10 s while the QRS complex was carefully checked for fusion or its loss.

The first stimulus was given 5 ms after the local electrogram at the pacing site so that the relation between the first stimulus, the local electrogram, and the QRS complex of the first non-paced VT complex remained constant.16,17

We used the criteria of transient entrainment defined by others.13,14 We focused on the local electrogram at the exit from the VT circuit. The criteria were (a) demonstration of constant fusion in the surface electrocardiogram during pacing at a constant rate faster than VT except for the last captured beat which occurred at the pacing rate in the surface electrocardiogram or in the local electrogram at the exit with the same non-fused configuration (non-fusion of the last captured beat); (b) demonstration of constant but different degrees of fusion in the QRS complex during pacing at a different pacing rate (progressive fusion); (c) demonstration of VT with localised exit block followed by the activation of that site from a different direction with a shorter conduction time by the next paced impulse (localised block).

DRUG ADMINISTRATION
Class I antiarrhythmic agents were tested. Drugs given empirically before the study that were ineffective were not tested.

Procainamide was administered usually first after the control study. The initial dose was 7–10 mg/kg, given intravenously at a rate of 50 mg a minute. After testing the first dose, an additional dose was given, but the total dose was 1000 mg or lower.16,17

When procainamide failed, mexiletine and disopyramide or cibenzoline were tested in that order. The initial dose of each was 300 mg/day for 1–2 weeks before the drug testing. An additional dose (100 mg/day) was given by mouth and the study was repeated 3–7 days later.

DEFINITIONS
● The block cycle length was defined as the longest paced cycle length that interrupted VT when rapid pacing was performed at progressively shorter cycle lengths in decrements of 10 ms.10,11
● The width of the zone of entrainment was defined as the difference between the cycle length of VT and the block cycle length.
● Sustained VT lasted for 30 seconds or longer and non-sustained VT lasted less than 15 beats.
● Responders were those in whom sustained VT was not induced after the final dose of the drug was given and up to the end of the whole protocol: the programmed stimulation protocol was the same before and after drug treatment.
● Non-responders were those in whom sustained VT was induced after the final dose of antiarrhythmic drugs was given and before the stimulation protocol was completed. If VT recurred 3–4 days after the start of drug treatment, that drug was considered a failure and drug testing was not attempted.
● The effective refractory period, which was measured at the pacing site, was the longest coupling interval that failed to capture the myocardium at a drive cycle length of 400 ms.

DATA ANALYSIS
The control and procainamide study were performed at the same sitting. When the test drug was given by mouth, the drug study was performed on a different day but the electrode catheters were positioned as closely as possible to those of the original study and rapid pacing was attempted from the same sites.

The cycle length of VT, the block cycle length, the width of the zone of entrainment and the effective refractory period were measured in the control state.

Next, drug-induced changes of these variables were assessed at the intermediate dose, and when VT was induced, an additional dose was given and induction of VT was attempted after the second dose.

The variables and their changes were compared between the tests with effective and
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non-effective drugs and factors related to non-inducibility at the final dose was assessed.

Values are presented as mean (SD). Statistical analysis was performed by a t test, and a P value less than 0.05 was regarded as significant.

Results

THE CONTROL STATE
VTs with a mean cycle length of 285 (43) ms were induced by two extrastimuli in eight patients. Seven VTs had a right bundle branch block configuration and one VT showed a left bundle branch block configuration. The earliest site of activation during VT was in the left ventricle in six and in the right ventricle in two. The local electrograms at the sites were found 15–120 ms before the inscription of the QRS complex.

TRANSIENT ENTRAINMENT OF VT
All VTs were entrained by rapid pacing from the right ventricular apex and both constant fusion and progressive fusion were confirmed in the surface electrocardiogram. As the paced cycle length was decreased, VT was interrupted at 231 (31) ms (fig 1). The width of the zone of entrainment was 54 (23) ms (fig 2).

During rapid pacing at the block cycle length, constant fusion was initially observed in the surface electrocardiogram and the local electrogram at the VT origin showed the same configuration as during VT. Then, constant fusion was lost abruptly and the local electrogram showed a change in configuration and activation time at that time (fig 1, bottom).

DRUG EFFICACY
The number of drug tests was 2.3 (0.7) and effective drugs that were able to suppress inducibility were confirmed in all eight patients: four with procainamide, one with cibenzoline, and three with mexiletine at the final dose.

In 10 other drug tests (procainamide in four, disopyramide in one, cibenzoline in two, and mexiletine in three), VT remained inducible at the final dose. Final doses for effective and the non-effective tests were similar: procainamide at 800 (163) mg v 850 (191) mg, mexiletine at 367 (58) mg v 365 (58) mg for responders and non-responders, respectively.
Figure 2 Drug-induced changes in the tests with effective drugs. Eighteen drug tests were attempted and VT was not induced at the final dose in eight tests in 8 patients.

At the intermediate doses (D1) the cycle length of VT (VTCL) was prolonged from 285 (43) ms to 367 (49) ms (P < 0.01) and the block cycle length (Block CL) was also prolonged from 231 (31) ms to 345 (47) ms (P < 0.01). The width of zone of entrainment (ZE) was narrowed from 54 (23) ms to 22 (13) ms (P < 0.02). After an additional dose, VT was not induced at the final dose (D2). C, control; NI, VT was not induced.

Changes of variables with effective drugs (fig 2)

At intermediate doses both the cycle length of VT (285 (43) ms to 367 (49) ms, P < 0.01) and the block cycle length (from 231 (31) ms to 345 (47) ms, P < 0.001) were prolonged. The block cycle length was more prolonged than the cycle length of VT (27 (15)% v 45 (15)%), respectively, (P < 0.01)). The width of the zone of entrainment was narrowed from 54 (23) ms to 22 (13) ms (P < 0.02).

Changes of variables with ineffective drugs (fig 3)

In the 10 tests in which VT was induced at the final dose, the cycle length of VT was prolonged from 285 (43) ms to 368 (36) ms (P < 0.01) at the intermediate dose (n = 6) and then to 382 (34) ms (P < 0.01) at the final dose (n = 10).

The block cycle length was prolonged from 231 (31) ms to 294 (26) ms (P < 0.01) at the intermediate dose (n = 6), then to 314 (35) ms (P < 0.01) at the final dose (n = 10). The drug-induced change in the cycle length of VT was not different from that of the block cycle length—that is, 28 (17)% v 26 (20)% and 33 (15)% v 34 (22)% at the intermediate and final dose, respectively.

The width of the zone of entrainment was 76 (8) ms and 75 (327) ms at the intermediate doses and the final doses respectively, and the changes were not significant (P > 0.1).

Comparisons of variables between effective and ineffective drugs

The cycle length of VT was no different at the intermediate dose for effective and ineffective drugs. The block cycle length was, however, longer at the intermediate dose with effective drugs than with ineffective drugs: 345 (47) ms v 294 (26) ms (P < 0.01).

The width of the zone of entrainment at the intermediate dose in the tests with effective drugs was narrower than that with ineffective drugs: 22 (13) ms v 76 (18) ms (P < 0.02).

The baseline effective refractory period was 244 (14) ms and 253 (23) ms in the tests with effective drugs and 253 (18) ms in the tests with ineffective drugs (NS).

Comparison of the effects of class IA and IB agents on VT

Both procainamide and mexiletine were tested in six patients. Procainamide and mexiletine prolonged the cycle length of VT from 273 (23) ms to 378 (57) ms and 367 (36) ms respectively and the block cycle length from 227 (31) ms to 287 (31) ms and 310 (53) ms respectively (P < 0.01). There was no significant difference in these two variables after treatment with procainamide (Ia) or mexiletine (Ib) in this small number of patients.

The zone of entrainment changed from 57 (27) ms to 91 (50) ms after procainamide and to 58 (35) ms after mexiletine admin-
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Discussion

PREVIOUS STUDIES

Some electrophysiological variables are thought to predict the efficacy of antiarrhythmic agents in reentrant VT. They include the baseline refractory period and the QT interval,\(^8\) the HV interval,\(^9\) drug-induced changes in the effective refractory period, or the duration of the paced QRS complex.\(^{10-23}\) However, these were based on studies of the normal myocardium\(^{14}\) and the response of abnormal myocardium to antiarrhythmic drugs is different.\(^{24-27}\)

ZONE OF ENTRAINMENT

We regarded constant fusion in the surface electrocardiogram as evidence that the tachycardia circuit was captured, entrained, and not terminated until it was lost during pacing at the block cycle length. Acceleration of the local electrogram at the site of VT origin to the pacing rate without a change in configuration was also used as evidence that VT was entrained.

Before VT was interrupted at a critical paced cycle length (block cycle length),\(^{3,5-9,10}\) both constant fusion and progressive fusion were observed at longer paced cycle lengths and the local electrogram at the site of VT origin was also accelerated to the pacing rate without a change in configuration.

During rapid pacing at the block cycle length, the local electrogram (fig 1, bottom) changed and simultaneously constant fusion in the surface electrocardiogram was lost.\(^{5,5-9,10}\) Such a change in the local electrogram associated with interruption of VT is Waldo et al's third criterion of transient entrainment\(^*\) and is explained by orthodromic block within the zone of slow conduction. The block cycle length may be regarded as the longest cycle length at which 1:1 conduction fails within the zone of slow conduction.

CHANGE OF ZONE OF ENTRAINMENT AND MECHANISM OF NON-INDUCIBILITY

The width of the zone of entrainment was defined as the difference between the cycle length of VT and the block cycle length and used as an index of the excitability gap.\(^{28}\) Significant narrowing of the zone of entrainment of VT at the intermediate doses of class I antiarrhythmic drugs was associated with subsequent non-inducibility of VT when an additional dose of the same drug was given.

It might therefore be postulated that if the block cycle length is prolonged and exceeds the cycle length of VT, the zone of entrainment will be obliterated and reentry will not be sustained.

Reentry was deemed to be suppressed when drugs prolonged the wave length beyond the path length or blocked some site within the area of slow conduction.\(^{29}\) Extreme narrowing of the zone of entrainment followed by non-inducibility after administration of additional doses of class I agents can be more easily explained by depression of conduction because the non-inducibility was achieved by Ib drug, mexiletine, which is known to shorten the duration of action potential.\(^{30,31}\)

Other mechanisms might be involved in suppressing the initiation of reentrant VT by drugs: inability to induce unidirectional block at a critical site, failure to establish an arc of functional block, or inability for the last paced wavefronts to enter the proximal limb of the slow path. However, these mechanisms are speculative and have to be tested.

LIMITATIONS

The excitable gap of VT should be determined using a single extrastimulus.\(^8\)\(^{12,13}\) It is often difficult to terminate VT with a single extrastimulus, however: VT is interrupted more efficiently with rapid pacing.\(^{5,5-9,11,12}\) Therefore, we have been using rapid pacing to study the electrophysiological characteristics of the zone of slow conduction.\(^{3,5-10,11}\)

The frequency and the number of stimuli might affect the electrophysiological properties of the zone of slow conduction, and the zone of entrainment might therefore wrongly estimate the excitable gap in some VTs.\(^{30}\)

When VT is interrupted, we regarded the longest cycle length that resulted in the failure of 1:1 conduction within the zone of slow conduction (orthodromic block) as the block cycle.\(^5\)\(^9-10\) Mechanisms other than orthodromic block might be involved in interruption of VT with rapid pacing,\(^{38}\) but such a mechanism remains to be established in human VT.

CONCLUSION

Drug tests were performed in eight patients at two doses of class I antiarrhythmic drugs. The width of the zone of entrainment was significantly narrowed at the intermediate doses only when effective drugs were tested, and the induction of VT was subsequently suppressed by an additional dose. The zone remained unchanged when ineffective drugs were tested and VT was induced after the administration of an additional dose of the test drug.

Drug-induced narrowing of the width of the zone of entrainment at the intermediate doses predicted the subsequent non-inducibility of VT.

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10.1136/hrt.75.2.165

Heart: first published as 10.1136/hrt.75.2.165 on 1 February, 1996. Downloaded from http://heart.bmj.com/ on June 9, 2022 by guest. Protected by copyright.

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