Procainamide-Induced Changes in Reentrant Ventricular Tachycardia with Special Reference to the Tachycardia-Interrupting Critical Paced Cycle Length during Transient Entrainment with Rapid Pacing

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SUMMARY

With rapid ventricular pacing, sustained ventricular tachycardia (VT) is often entrained and interrupted at a critical paced cycle length. In this paper, the possible mechanism and determinant of the critical cycle length interrupting VT are addressed.

Sixteen consecutive patients underwent rapid ventricular pacing in 18 morphologically distinct sustained VTs before and after procainamide. The VT morphology was identical before and after the drug.

The VT origin was determined by endocardial mapping as the earliest site of activation of VT and an electrode catheter was located at the site. Rapid pacing was performed to entrain VT and repeated in 10 msec decrements of cycle length until VT was interrupted at a critical paced cycle length which was defined as the block cycle length.

The effective refractory period was measured at the pacing site. The paced QRS duration and the local conduction time were measured and used as indices of conduction time in the normal myocardium.

VT was entrained and interrupted in all patients. At the block cycle length, initial constant fusion was replaced abruptly by the fully paced QRS complex. At the same time, the local electrogram at the site of VT origin showed changes in the morphology and the timing of activation which were identical to those of the fully paced beat. This loss of fusion and the changes in the local electrogram were considered to be a result of orthodromic block and the block cycle length was assumed to represent the cycle length at which 1:1 conduction fails in the area of slow conduction.

After procainamide, both the VT cycle length and the block cycle length were prolonged to a similar degree (p < 0.001) but the relative degree of
change varied from patient to patient. The paced QRS duration and the conduction time were prolonged by procainamide but in smaller degrees than the cycle length of VT or the block cycle length \((p < 0.02-01)\). The effective refractory period at the pacing site and the QT interval showed small changes after procainamide.

The postrepolarization refractoriness rather than the duration of action potential can be responsible for the procainamide-induced prolongation of the block cycle length, and the block cycle length might be used as a new index to characterize the electrophysiologic property of the VT circuit and also the action of antiarrhythmic drugs. (Jpn Heart J 35: 611–623, 1994)

**Key words:** Ventricular tachycardia Transient entrainment Zone of slow conduction Block pacing cycle length Refractoriness

**MOST** sustained ventricular tachycardias (VT) including those unrelated to coronary artery disease have been shown to be entrained with rapid ventricular pacing, indicating the presence of a reentrant circuit with an excitable gap as the underlying mechanism.

When rapid pacing was repeated at progressively shorter cycle lengths, VT was interrupted at a critical cycle length and the interruption of VT was always associated with the change in the local electrogram at the earliest site of activation of the VT, the third criterion of transient entrainment by Waldo. The abrupt loss of fusion was also observed on the surface electrocardiogram when VT was interrupted.

We defined the critical paced cycle length as the block cycle length, since such characteristic changes in the local electrogram and surface electrocardiogram suggest a failure of orthodromic 1:1 conduction in the slow conduction zone within the reentrant circuit.

In the present study, we investigated the effects of procainamide on the entrainment of monomorphic sustained VT in order to obtain further insight into the determinant of the block cycle length.

## Subjects and Methods

**Patient selection:** Sixteen consecutive patients with symptomatic sustained VT who underwent electrophysiologic study were included.

The selection criteria were as follows: (1) VT with an identical QRS configuration was induced by programmed ventricular stimulation before and after procainamide. (2) VT was entrained with rapid ventricular pacing and finally interrupted at a critical paced cycle length when rapid pacing was performed as described below.

The age ranged from 14 to 77 years and the mean was 50 ± 20 years. Nine
patients were male and seven were female.

Six patients had VT related to coronary artery disease and all of them had remote myocardial infarction. Occlusion of the coronary artery to the infarction area was confirmed by coronary angiography. Two patients (one male and one female) had been operated on for tetralogy of Fallot 8 and 15 years previously. One male and one female had been operated on for double outlet right ventricle 7 and 12 years previously, respectively. Two patients had idiopathic cardiomyopathy. In the remaining four patients, arrhythmogenic right ventricular dysplasia was diagnosed in one, pulmonic regurgitation of unknown cause in one, progressive systemic sclerosis in one and no demonstrable heart disease in one. Verapamil-responsive idiopathic VT was not included.

Electrophysiologic study: The procedure, the purpose and possible risks were fully explained and after informed and written consents were obtained, the electrophysiologic study was performed in the postabsorptive and non-sedated state. All antiarrhythmic agents were discontinued for two to three days before the control study and no patient had been treated with amiodarone.

Quadrupolar electrode catheters (USCI, 6F multipurpose catheter, Boston, MA, USA) were placed against the right atrium, the His-bundle region, and the apex or the outflow tract of the right ventricle. Another quadrupolar electrode catheter was positioned within the left ventricle. The site of VT origin was determined by extensive endocardial catheter mapping as the earliest site of activation during VT, and an electrode catheter was placed at the site.

Induction of VT: The standard protocol was used for the induction of VT: the extrastimulus technique using 1–2 (3 when necessary) extrastimuli after eight basic stimuli at two cycle lengths, 600 msec and 400 msec, and incremental pacing at a cycle length between 600 and 286 msec for 5–10 seconds. They were delivered at two sites in the right ventricle and one site in the left ventricle. Electrical stimuli of 2.0 msec duration were delivered at twice the late diastolic threshold by a programmable stimulator (Fukuda Denshi Cardiac Stimulator BCO2, Tokyo, Japan). The intracavitary electrograms were filtered at 30 to 500 Hz and stored on magnetic tape (TEAC Cassette Data Recorder XR-5000, Tokyo, Japan) simultaneously with surface electrocardiographic leads I, II and VI. They were retrieved later on a recorder (Fukuda Denshi Co., Thermal Recorder RF-85, Tokyo, Japan). The data were also recorded directly on an ink-jet recorder (Siemens-Elema Mingograf 7) at a paper speed of 100 mm/sec. All induced arrhythmias were recorded on a 12 lead electrocardiogram.

Rapid pacing during VT: After the induction of VT, rapid pacing was performed from the apex of the right ventricle starting at a cycle length which was 10–20 msec shorter than that of the VT, and repeated in decrements of 10 msec until VT was interrupted.
The criteria of transient entrainment by earlier workers were used: (1) demonstration of a constant fusion during pacing at a constant rate faster than the VT except for the last captured beat which occurred at the pacing rate on the surface electrogram or on the intracavitary electrogram with the same non-fused morphology (non-fusion of last captured beat), (2) demonstration of a constant but different degree of fusion in the QRS complex during pacing at a different pacing rate (progressive fusion), (3) interruption of VT with localized block at a site or sites followed by activation of that site or sites from a different direction with a shorter conduction time by the next paced impulse. If VT was not entrained from the apex of the right ventricle, rapid pacing was performed from the outflow tract of the right ventricle. If VT was not entrained from the two sites, rapid pacing was attempted from the left ventricle.

The first stimulus was given 5 msec after triggering of the local electrogram at the pacing site so that the relation between the first stimulus and the local electrogram or the QRS complex of VT was always constant for each pacing. Each rapid pacing was continued for 5–10 seconds and the QRS complexes and presystolic electrograms were checked for possible changes in the morphology and timing of the activation. Actually, constant fusion was obtained within several paced beats, and when VT was interrupted, sudden changes in the presystolic electrogram or sudden loss of fusion in the surface electrocardiogram was observed within 5 pacing stimuli as reported earlier.

Direct current shock was employed to restore sinus rhythm when acceleration of the VT rate or hemodynamic deterioration was observed. The effective refractory period and Q-T interval: The effective refractory period of the normal myocardium was measured at the pacing site by the extrastimulus technique of giving premature stimuli at progressively shorter coupling intervals until they failed to capture the myocardium. The longest coupling interval which failed to capture the myocardium was defined as the effective refractory period. The basic drive was given at a cycle length of 400 msec. The QT interval was measured and the effect of procainamide was compared with that of other variables.

The paced QRS duration and local conduction time: The paced QRS duration was measured at a paced cycle length of 400 msec and used as an index of the global conduction time of the ventricle. The local conduction time was also measured from the stimulus to the VT origin or to a remote site of the contralateral ventricle. These parameters were measured just prior to the induction of VT or soon after the termination of VT and used as conduction times in the normal myocardium.

Drug administration: Procainamide was given intravenously at 12–15 mg/kg at a rate of 50 mg/minute after the control electrophysiologic study.
**Analysis of data:** In the control study, the VT cycle length, the block cycle length and the effective refractory period at the pacing site were measured.

When VT with the same morphology as the control was induced after the administration of procainamide, the drug-induced change in the block cycle length and the VT cycle length were determined. The block cycle length, the VT cycle length and their changes were compared.

Alterations in the drug-induced changes of the effective refractory period, the paced QRS duration and the conduction time were compared with those of the cycle length of VT or the block cycle length. The QT interval was also measured before and after procainamide.

Values are presented as mean ± S.D. Statistical analysis was performed by a t-test, and a p-value of less than 0.05 was considered significant.

**RESULTS**

**Induction and entrainment of VT:** According to the criteria of patient selection, VT was induced in all patients. A right bundle branch block-pattern was

**Table 1.** Clinical and Electrophysiologic Characteristics of Ventricular Tachycardia and Their Drug-induced Changes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>UDH</th>
<th>VT*</th>
<th>VTCL/Block CL</th>
<th>C</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72M</td>
<td>OMI</td>
<td>RB</td>
<td>280/220</td>
<td>320/270</td>
<td>1000</td>
</tr>
<tr>
<td>2</td>
<td>72M</td>
<td>OMI</td>
<td>RB</td>
<td>340/280</td>
<td>420/380</td>
<td>600</td>
</tr>
<tr>
<td>3</td>
<td>70M</td>
<td>OMI</td>
<td>RB</td>
<td>260/220</td>
<td>370/260</td>
<td>600</td>
</tr>
<tr>
<td>4</td>
<td>43F</td>
<td>DM, OMI</td>
<td>RB</td>
<td>240/180</td>
<td>350/310</td>
<td>800</td>
</tr>
<tr>
<td>5</td>
<td>77F</td>
<td>OMI</td>
<td>RB</td>
<td>260/200</td>
<td>310/240</td>
<td>600</td>
</tr>
<tr>
<td>6</td>
<td>60M</td>
<td>OMI</td>
<td>RB</td>
<td>375/320</td>
<td>430/390</td>
<td>600</td>
</tr>
<tr>
<td>7</td>
<td>46M</td>
<td>DCM</td>
<td>RB</td>
<td>370/300</td>
<td>440/340</td>
<td>1000</td>
</tr>
<tr>
<td>8</td>
<td>51F</td>
<td>DCM</td>
<td>RB</td>
<td>400/290</td>
<td>540/470</td>
<td>600</td>
</tr>
<tr>
<td>9</td>
<td>28F</td>
<td>T/F</td>
<td>LB</td>
<td>370/280</td>
<td>445/300</td>
<td>400</td>
</tr>
<tr>
<td>10</td>
<td>14M</td>
<td>T/F</td>
<td>LB</td>
<td>380/240</td>
<td>520/310</td>
<td>300</td>
</tr>
<tr>
<td>11</td>
<td>16M</td>
<td>DORV</td>
<td>LB</td>
<td>270/220</td>
<td>320/270</td>
<td>600</td>
</tr>
<tr>
<td>12</td>
<td>21F</td>
<td>DORV</td>
<td>LB</td>
<td>260/220</td>
<td>445/300</td>
<td>600</td>
</tr>
<tr>
<td>13</td>
<td>55M</td>
<td>ARVD</td>
<td>LB</td>
<td>430/250</td>
<td>500/400</td>
<td>800</td>
</tr>
<tr>
<td>14</td>
<td>60F</td>
<td>PR</td>
<td>LB</td>
<td>430/250</td>
<td>480/360</td>
<td>600</td>
</tr>
<tr>
<td>15</td>
<td>54F</td>
<td>PSS</td>
<td>LB</td>
<td>260/240</td>
<td>410/360</td>
<td>600</td>
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<tr>
<td>16</td>
<td>57M</td>
<td>none</td>
<td>LB</td>
<td>300/250</td>
<td>400/320</td>
<td>600</td>
</tr>
</tbody>
</table>

50±20

| 321±63/245±35 | 414±68/332±56 |

ARVD = arrhythmogenic right ventricular dysplasia; Block CL = block cycle length; C = control; DCM = dilated cardiomyopathy; DM = diabetes mellitus; DORV = double outlet right ventricle; LB = left bundle branch block-like morphology; OMI = old myocardial infarction; PR = pulmonic regurgitation; PSS = progressive systemic sclerosis; RB = right bundle branch block; T/F = Tetralogy of Fallot; UDH = underlying heart disease; VT* = VT-morphology; VTCL = the cycle length of VT; RB** = morphologically distinct VT.
found in 10 VTs of 9 patients and a left bundle branch block-pattern in 8 VTs of 8 patients. VT with two morphologies was induced in two patients. The cycle length of VT was 321 ± 63 msec (Table I).

VT was entrained with rapid pacing from the right ventricular apex in 14 VTs and from the outflow tract in 4 VTs and interrupted at the mean cycle length of 245 ± 35 msec. At longer paced cycle lengths, constant fusion and progressive fusion were demonstrated (Figures 1 and 2).

There was a fair correlation between the VT cycle length and the block cycle length in the control state \( r = 0.70, p < 0.005 \).

** Interruption of VT:** During rapid pacing at the block cycle length, constant fusion was initially observed but it was replaced by the fully paced complex (Figures 1, 2, and 3). At the same time, the local electrogram at the VT origin showed a change in the morphology and timing of activation (Figure 3). These changes were always followed by interruption of VT as evident after the cessation of rapid pacing.

The changes in the surface electrogram and the local electrogram associated with the interruption of VT were considered to be the result of orthodromic

![Figure 1](image-url). Rapid pacing and interruption of VT. Patient is case 11 and had VT in the postoperative state of double outlet right ventricle. In the control evaluation, VT with a cycle length of 270 msec was induced and rapid pacing was performed at 260–220 msec. In A, constant fusion is evident. At a cycle length of 220 msec, constant fusion was observed except for the last four beats as shown by asterisks in B. The last four beats were identical to the fully paced configuration of the QRS complex. After procainamide, the cycle length of VT was prolonged to 320 msec (C) and interrupted at 270 msec. A similar abrupt change into the fully paced configuration was observed at a block cycle length of 270 msec (D). I, II, VI = surface leads. RVA = the apex of the right ventricle (pacing site).
block in the area of slow conduction of the reentrant circuit; i.e. the localized block by Waldo.1

Effects of procainamide on VT: In all 18 VTs of 16 patients, VT with the QRS morphology identical to the control was induced after procainamide. The VT cycle length was, however, prolonged from 321 ± 63 to 414 ± 68 msec after procainamide ($p < 0.001$) (Figure 4); the percentage increase was 31 ± 17\% (Table II).

The block cycle length was also prolonged from 245 ± 35 to 332 ± 56 msec after procainamide ($p < 0.001$) (Figure 4); the mean increase was 33 ± 18\% and ranged from 20 to 180 msec (Table II).

A positive correlation between VT cycle length and block cycle length ($r = 0.72$, $p < 0.001$) was also observed after procainamide. The prolongation of the VT cycle length was independent of that of the block cycle length as shown in Figure 5.
The effective refractory period and Q-T interval: The effective refractory period measured at the pacing site was 224 ± 21 before and 242 ± 20 msec after procainamide; the change was 6 ± 3% (p < 0.01). Though simple comparison was not warranted, it was smaller than that of the cycle length of VT or the block cycle length (Table II).

The QT interval was prolonged from 0.390 ± 0.038 to 0.410 ± 0.053 sec and the corrected QT interval was prolonged from 0.428 ± 29 to 0.482 ± 44 sec\(^{1/2}\) (p < 0.01), but the change was smaller than that of the block cycle length (p < 0.02).

The paced QRS duration and local conduction time: The paced QRS duration was prolonged from 180 ± 32 to 205 ± 36 msec at the time of VT induction, and the change was significant (p < 0.001). The change was, however, significantly smaller than that of the VT cycle length or the block cycle length; 14 ± 17% vs. 31 ± 17% (p < 0.02).

The local conduction time was prolonged from 82 ± 15 msec to 91 ± 17 msec (p < 0.001) and the change (11 ± 5%) was smaller than that of the VT cycle length (p < 0.02) (Table II).
Figure 4. Procainamide-induced changes of VT cycle length and block cycle length. After procainamide, VT cycle length (VTCL) was prolonged from 321 ± 63 to 414 ± 68 msec \( (p < 0.001) \). Block cycle length (Block CL) was also prolonged to a similar degree; from 245 ± 35 to 332 ± 56 msec \( (p < 0.001) \).

Table II. The Drug-induced Changes of Electrophysiologic Parameters

<table>
<thead>
<tr>
<th></th>
<th>VTCL</th>
<th>Block CL</th>
<th>Paced QRS</th>
<th>CT</th>
<th>ERP</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Changes</td>
<td>31±17%</td>
<td>33±18%</td>
<td>14±17%*</td>
<td>11±5*</td>
<td>6±3%**</td>
</tr>
</tbody>
</table>

*: \( p < 0.02 \) vs. VTCL and \( p < 0.02 \) vs. Block CL. **: \( p < 0.001 \) vs. VTCL and Block CL. VTCL = VT cycle length; Block CL = the block cycle length; Paced QRS = the paced QRS duration; CT = the local conduction time.

**DISCUSSION**

Mechanism of the interruption of VT: With rapid ventricular pacing, all VTs were entrained and interrupted at a critical cycle length which was defined as the block cycle length.\(^7,^{13}\) The findings at the block cycle length were characterized as follows; (1) constant fusion was found in the initial phase but lost subsequently (Figures 1 and 2), (2) the local electrogram at the VT origin showed changes in the morphology and the timing of activation (Figure 3), (3) these changes were invariably associated with the interruption of VT as evident after the cessation of rapid pacing. The finding is indeed the third criterion of transient entrainment by
Figure 5. Comparisons of the procainamide-induced change of the VT cycle length and the block cycle length.

Though the overall changes in the VT cycle length (VTCL) and the block cycle length (Block CL) were not different, the individual response of each parameter was variable; in 8 VTs the block cycle length was prolonged more than the VT cycle length and in another 10 VTs, the reverse was found. A similar relation was observed in the percentile changes between the VT cycle length and the block cycle length. The significance of the different response of each parameter is unknown thus far.

Waldo\(^1\) and orthodromic block in the area of slow conduction has been considered to be responsible for the changes and the interruption of VT\(^1,7,8\). If the block cycle length represents the longest paced cycle length which results in orthodromic block, it might be used as a new index to quantify the action of antiarrhythmic drugs on the reentrant circuit as well as to characterize the electrophysiologic property of the VT circuit.

**Determinant of the block cycle length:** In normal cardiac tissues, in which excitation depends on the fast sodium channel, the refractory period under physiological conditions is determined primarily by the duration of the action potential because of a quick recovery of sodium channel availability after full repolarization.\(^{14\text{-}15}\)

Thus far, the duration of the action potential of the tissue of the VT circuit has been considered as characterizing the conductive property of the VT circuit and the length of the excitable gap.\(^{16,17}\) At the block cycle length the wave fronts entering the area of slow conduction might encounter tissues which are refractory and might be blocked.

In the control state, the block cycle length was close to the effective refractory period; 245 ± 35 vs. 224 ± 21 msec. After procainamide, the block cycle length was, however, prolonged markedly to 332 ± 56, an increase of 33 ± 18%.
Though procainamide blocks the potassium channel and prolongs the duration of the action potential,\textsuperscript{14,18} it would be unlikely that the prolongation of the block cycle is a result of the prolonged duration of the action potential. Otherwise, a marked prolongation of the Q-T interval would be expected, but such was not the case. Our preliminary finding (Aizawa et al. data in preparation) suggests that the block cycle length is also prolonged by mexiletine which is known to shorten the duration of the action potential.\textsuperscript{18-19}

In the presence of Class-I antiarrhythmic drugs, the recovery of the maximum upstroke velocity of the action potential or sodium inward current lags behind completion of repolarization especially at higher frequencies.\textsuperscript{15,19-21} Indeed, quinidine and procainamide were long ago shown to prolong the refractory period well beyond the duration of the action potential when the parameter was measured by the maximum follow frequency.\textsuperscript{22,23}

From these discussions the block cycle length must be closely related to the post-repolarization refractoriness rather than the duration of the action potential. The effect of procainamide on the conduction: VT induced after procainamide showed a significantly prolonged cycle length with an increase of 31±17%. On the other hand, the paced QRS duration which can represent an index of the global ventricular activation showed a smaller change than that of the VT cycle length with an increase of 14 ± 17 vs. 31 ± 17% after procainamide ($p < 0.02$). The local conduction showed a smaller prolongation, 11 ± 5%.

Since the VT cycle length indicates the revolution time of the wave fronts along the reentrant circuit, it reflects mainly the conduction velocity in the area of slow conduction. On the other hand, the paced QRS duration or the local conduction time reflects the conduction time through the normal myocardium. The difference of the drug-induced change between the VT cycle length and the paced QRS duration or the local conduction time suggests a preferential action of procainamide on the VT circuit as reported earlier.\textsuperscript{24-25}

Limitations: The present study has several limitations. First, we treated VT associated with various underlying heart diseases. However, VT unassociated with coronary artery disease was shown to be entrained\textsuperscript{7,8,13} and the most likely mechanism would be reentry.

In the present study, only VT which remained inducible after drug administration was studied and the result does not give any insight into the mechanism by which drugs suppress inducibility. Characteristic changes of these parameters in VT in relation to the efficacy of antiarrhythmic agents are to be studied.

The extrastimulus technique might be used to evaluate the refractoriness of the zone of slow conduction,\textsuperscript{6,16,17} but it is often difficult to interrupt VT with a single extrastimulus.\textsuperscript{6} This is the reason that we employed rapid pacing to interrupt VT. If the block cycle length is related to postrepolarization refractoriness,
however, it might be affected by the number of stimuli, and such is to be systematically determined.

**Conclusion:** VT with an identical morphology was entrained and interrupted before and after procainamide at a critical cycle length (block cycle length) when the paced cycle length was decreased in steps of 10 msec. Characteristic changes observed at the block cycle length suggest that orthodromic block is the cause of interruption of VT and the block cycle length can be a critical cycle length at which 1:1 conduction fails in the VT circuit.

A marked prolongation of the block cycle length would be well explained if the determinant of the block cycle length is the postrepolarization refractoriness rather than the duration of the action potential. A smaller change in the conduction time through the normal myocardium or in the paced QRS duration than that of the cycle length of VT suggests a preferential action of procainamide on the area of slow conduction of the VT circuit.

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