Effects of Heptanol, Class Ic, and Class III Drugs on Reentrant Ventricular Tachycardia

Importance of the Excitable Gap for the Inducibility of Double-Wave Reentry

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Background Double-wave reentry (DWR) can be a mechanism for acceleration of ventricular tachycardia (VT) with a large excitability gap (EG). The purpose of this study was to determine the effects of heptanol, class Ic, and class III drugs on the inducibility of DWR.

Methods and Results In 11 Langendorff-perfused rabbit hearts, a thin ring of anisotropic left ventricular epicardium was created by a cryoprobe. VT with a revolution time of 180±26 milliseconds and an EG of 106±8 milliseconds was induced by incremental pacing. During control, entrainment with 10 stimuli at a 99±15-millisecond interval terminated VT in seven hearts. In four hearts VT was accelerated from 205±24 to 115±14 milliseconds by introduction of a second circulating wave in the ring. In the seven VTs that could not be accelerated, 0.5 μmol/L Org7797 (class Ic) and 1.0 mmol/L heptanol (uncoupling agent) prolonged the cycle length of VT by 32% and 37%, respectively.

In addition to the beneficial effects of antiarrhythmic drugs and overdrive stimulation, aggravation of preexisting arrhythmias and/or provocation of new arrhythmias have been reported. In 36% of patients with ventricular tachycardia (VT) after myocardial infarction, overdrive stimulation had a proarrhythmic effect, while electrophysiological studies in patients on antiarrhythmic drugs showed an 18% incidence of proarrhythmias.

A number of experimental studies have elucidated some of the mechanisms of proarrhythmia during overdrive stimulation and antiarrhythmic drug therapy. In previous investigations from our laboratory, it has been shown that acceleration of VT by overdrive pacing can be caused either by a change in reentrant circuit or by induction of a second wave in the same circuitous pathway (double-wave reentry). Double-wave reentry could only be induced in relatively slow VTs with a large excitability gap. We hypothesized that antiarrhythmic drugs might promote or inhibit the inducibility of double-wave reentry by affecting the length of the excitability gap during VT. In the present study we investigated the effects of electrical uncoupling and class Ic and class III effects both on the excitability gap and the susceptibility to overdrive pacing–induced acceleration of VT. Our results show that both class Ic drugs and uncoupling agents increase the likelihood of induction of double-wave reentry by enlarging the excitability gap during VT. On the other hand, class III drugs may prevent acceleration by shortening the excitability gap during VT.

Conclusions Drugs that increase the ratio of EG and RP enhance the susceptibility to acceleration of VT, whereas drugs that decrease this ratio prevent induction of sustained double-wave reentry. (Circulation. 1994;90:1012-1022.)

Key Words • anisotropy • reentry • entrainment • antiarrhythmic drugs • excitability gap

Preparation

Eleven Flemish Giant rabbits (weight, 4.0±0.4 kg) were used for this study. Animal preparation and handling was performed according to the guiding principles of the American Society of Physiology and approved by the Animal Investigation Committee of the University of Limburg. The rabbits were anesthetized with 0.5 mg/kg IM of Hypnorm (10 mg Fluanison and 0.2 mg Phentanylm/L). After heparinization (1000 IU IV), the rabbits were killed by cervical dislocation, the heart was quickly removed, and the aorta was connected to a Langendorff perfusion system. The hearts were perfused by Tyrode’s at 37°C with a constant pressure of 60 mm Hg, resulting in a flow of 27±7 mL/min. The composition of the Tyrode’s (in mmol/L) was as follows: NaCl 130.0, NaHCO₃ 20.1, NaH₂PO₄ 1.2, KCl 4.0, CaCl₂ 2.2, MgCl₂ 0.6, and glucose 12.0. The Tyrode’s was saturated with Carbogen (95% O₂ and 5% CO₂); pH was 7.35. Thin epicardial layers of anisotropic ventricular myocardium were obtained by a cryoprobe, as described previously. In brief, a cryoprobe was inserted in the right ventricular cavity and filled with liquid nitrogen.
(−192°C) until the total right ventricle was frozen. The probe was then inserted in the left ventricular cavity, the heart was immersed in a tissue bath containing Tyrode’s of 30°C, and the coronary flow was temporarily interrupted. Subsequent filling of the cannula with liquid nitrogen for 7 minutes destroyed the endocardial four-fifths part of the left ventricle. After the cryoprocedure, the flow was restored and the heart was emerged from the tissue bath. By this technique a thin, Langendorff-perfused, two-dimensional sheet of anisotropic left ventricular subepicardium (thickness, 1.0±0.4 mm) was obtained showing normal conduction velocities and refractory periods.10 In this sheet of subepicardium, a central obstacle was created parallel to the left anterior descending coronary artery (LAD) by an epicardial cryoprobe (20×2 mm).11 In the resulting ring of perfused myocardium, sustained reentrant VT was induced by programmed electrical stimulation. During VT, a fully excitable gap was present at each site in the circuit, the width being determined by the difference between the cycle length of the VT and the local refractory period. As described previously,11 the conduction velocity varied in different segments of the ring. At the base and the free wall, conduction velocity was relatively fast because impulse propagation was parallel to the epicardial fiber direction. In contrast, in the corridor between the LAD and the obstacle, propagation, the conduction velocity was much slower due to propagation transverse to the epicardial fiber direction. At the apex, the relation between conduction velocity and fiber direction could not be reliably determined.11 The large distance between subsequent isochrons in this area overestimates the true conduction velocity because at the apex, the inter-electrode distances are distorted due to the two-dimensional projection of the electrode array.

**Recording**

A spoon-shaped mapping electrode molded to the epicardial surface of the left ventricle containing 248 silver electrodes (diameter, 0.3 mm; interelectrode spacing, 2.25 mm) was used to map the ventricular activation. The characteristics of the mapping system have been described elsewhere.12 After amplification and filtering (bandwidth, 1 to 400 Hz), the electrograms were multiplexed (sampling rate, 1 kHz) and AD converted (8 bits). An algorithm for automatic detection of the intrinsic negative deflections in the electrograms was used to determine the local activation times and to generate color-coded activation maps. Interactive editing of activation times was performed if necessary.

From the activation maps, longitudinal conduction velocity (θL) was determined at the base and the left free wall of the left ventricle; transverse conduction velocity (θT) was measured at the corridor between the LAD and the central obstacle.11,13 Ideker et al14 have pointed out that in intact three-dimensional ventricles, measurement of the true epicardial conduction velocity is only possible if the angle of the propagating wave front relative to the epicardium is known. Otherwise, when the angle of the wave front is oblique with the plane of measurement, the conduction velocity would be greatly overestimated. However, in our model of a two-dimensional layer of subepicardium (thickness ±1mm) the wave front was forced to propagate in the same plane as the mapping plane. An additional prerequisite for accurate measurements is that the axis between the pair of recording sites, between which conduction velocity is measured, is oriented parallel to the direction of propagation. This prerequisite was fulfilled by careful selection by eye of two recording sites oriented at an angle of 90° relative to the wave front as determined by the average contour of all intervening isochrons (Fig 1). During very slow conduction as caused by the administration of drugs, the electrode spacing of 2.25 mm may have been too large to identify zig-zag conduction between adjacent electrode sites.15 Under these conditions, the measured value may no longer represent true conduction velocity and the term apparent conduction velocity is more appropriate.16

**Drug Infusion**

Heptanol (Merck), Org77977 (Orgaran), and D-sotalol (Bristol-Myers) were dissolved in Tyrode’s and added to the perfusion fluid by an infusion pump. The effective concentrations were heptanol 1.0 mmol/L, Org77977 0.5 μmol/L, and D-sotalol 35 μmol/L (10 mg/L). A 30-minute equilibration time was allowed before testing the electrophysiological effects of each drug. Heptanol and Org77977 were tested separately in two hearts and sequentially in three hearts. In these three hearts, heptanol was administered first because it was washed out more easily than Org77977. D-Sotalol was administered separately in four other hearts.

**Stimulation**

A computer-controlled stimulator (Medtronic SP3084) was used for bipolar stimulation at any pair of electrodes selected from the mapping electrode. Sustained monomorphic VT around the obstacle was induced by incremental pacing. Reset and entrainment of VT was performed at three pacing sites around the ring: at the base, the free wall, and the apex of the left ventricle. Both during control and during infusion of Org77977, D-sotalol, and heptanol, the same pacing protocol was performed. In those hearts in which heptanol and Org77977 were tested sequentially, control measurements were performed before Org77977 was infused.

During VT, the effective refractory period (ERP) at three different sites around the ring was measured by applying a single premature stimulus after 20 VT beats. A stimulus strength of four times threshold was used to elicit premature beats early in the relative refractory period. Diastolic threshold was determined during VT both during control and during administration of drugs. An electrogram recorded adjacent to the pacing site was used to synchronize the stimulator. The coupling interval between activation of this reference electrogram (V) and the stimulus (S) was shortened in steps of 2 milliseconds. The ERP was determined as the longest VS interval that failed to initiate a propagated response. The activation times of the recording electrograms around the pacing site showed that the propagated response always originated from the actual site of pacing and not at a remote site. After the experiment, the actual coupling interval at the site of pacing was determined by interpolating the VS intervals around the pacing site. The return cycle was determined as the interval between the stimulated activation and the subsequent nonpaced activation close to the site of pacing during regular VT.

Entrainment of VT was performed by applying trains of 10 stimuli (four times threshold) at pacing intervals shorter than the VT interval. The first stimulus did not always capture the ventricle because stimulation was started at random. However, in that case the second stimulus always captured VT, resulting in at least nine entraining stimuli. The entrainment protocol was started with pacing intervals being 5 to 10 milliseconds shorter than the VT interval. The pacing interval then was shortened in steps of 10 milliseconds until VT was either terminated, changed in morphology, or accelerated. During each VT, about eight different rates of entrainment were tested.

**Statistical Analysis**

Results were compared using the paired Student’s t test, ANOVA, and Bonferroni’s t test when appropriate. Probabil- ity values of <.05 were taken as statistically significant.

**Results**

**Characteristics of VT and Entrainment During Control**

In 11 experiments, VT was based on either a clockwise (n=8) or a counterclockwise (n=3) circulating wave front
around the central anatomical obstacle. VTs were long-lasting and stable, with a variation in cycle length of less than 2 milliseconds. The cycle length of the 11 VTs ranged from 153 to 245 milliseconds, with a mean of 180±26 milliseconds (Table 1). During VT, the conduction velocity in different segments of the ring was not the same. In the corridor between the LAD and the central obstacle, propagation was slow (20±3 cm/s, n=11) because of conduction transverse to the epicardial fiber orientation. At the base and the free wall, the impulse traveled parallel to the fiber direction with a velocity of about 74±9 cm/s (n=11). The cycle length of VT was determined mainly by the size of the central obstacle and the length of the area of slow conduction. In VTs with a long cycle length, the segment of slow conduction was longer than in VTs with a short cycle length.11

During VT, the ERP was determined by applying single premature stimuli at the base, the free wall, and the apex of the left ventricle. The maximal spatial difference in refractory periods in 11 VTs was 5±3 milliseconds (range, 2 to 12 milliseconds). There was no anatomically defined area in the ventricle with a systematically longer or shorter refractory period. The average refractory period during 11 VTs was 106±11 milliseconds, with an excitable gap of 74±17 milliseconds. None of the 11 VTs could be terminated by single premature stimuli.

Entrainment of VT with 10 stimuli was performed at the same pacing sites where the refractory periods were determined. At longer pacing intervals, VT was transiently entrained but resumed its normal activation pattern after cessation of pacing. Entrainment at short pacing intervals (99±15 milliseconds) resulted in termination of VT in 29 of 33 cases. Termination was due to conduction block of one of the paced orthodromic waves, as described previously by Boersma et al.13 In 4 of 33 cases (four hearts) entrainment accelerated VT from 205±24 to 115±14 milliseconds. Mapping of the accelerated VT showed two excitation waves traveling simultaneously in the same direction around the central obstacle, previously described as double-wave reentry.5 Because of conduction velocity depression of the two circulating waves during the accelerated VT, the cycle length of double-wave reentry was always slightly longer than half the cycle length during single-wave reentry.

**Effects of Org7797 and Heptanol on VT**

In 7 hearts in which VT could not be accelerated during control, 0.5 μmol/L of the experimental class Ic drug Org7797 and 1.0 mmol/L of heptanol were administered. Fig 1 shows a representative example of the effects of Org7797 and heptanol on VT. During control, the impulse circulated clockwise around the central obstacle with a cycle length of 172 milliseconds. Longitudinal (εL) and transverse (εT) conduction velocities were 87 and 20 cm/s, respectively, with an anisotropy ratio (εL/εT) of 4.4. Both Org7797 and heptanol slowed

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**Fig 1.** The effects of Org7797 and heptanol on reentrant ventricular tachycardia (VT). The cycle length of the clockwise VT was 172 milliseconds during control and increased to 219 milliseconds during Org7797 and to 235 milliseconds during heptanol. This was due to a depression of both longitudinal and transverse conduction. The two arrows indicate the sites around the ring at which longitudinal and transverse conduction velocities were measured. Electrograms at the top show the earliest premature stimulus eliciting a propagated response. Bars below the maps show the average effective refractory period (ERP) and excitable gap (EG) during VT, measured as the average value at three different sites around the ring. Activation times are given in milliseconds; isochrons are drawn at 10-millisecond intervals. Calibration bar=5 mV. See text for discussion.
VT, increasing the VT interval to 219 and 235 milliseconds, respectively. Org7797 almost equally depressed $\theta_t$ and $\theta_L$ to 73 and 16 cm/s, respectively (anisotropy ratio, 4.6). In contrast, heptanol depressed $\theta_t$ much more than $\theta_L$, increasing the anisotropy ratio to 5.9. During heptanol, $\theta_t$ was 82 cm/s and $\theta_L$ was 14 cm/s. The electrograms above the activation maps show the earliest stimuli that reset VT both during control and during administration of Org7797 and heptanol. As can be seen, the shortest possible interval induced by premature stimulation prolonged only slightly during Org7797 and heptanol from 114 to 123 and 122 milliseconds. The bars below the maps show the effects on the ERP and the excitable gap (EG) during tachycardia. Org7797 and heptanol increased the excitable gap from 70 milliseconds to 111 and 126 milliseconds, respectively.

Table 2 gives the average effects of Org7797 and heptanol for all experiments. Infusion of Org7797 (n=5) prolonged the cycle length of VT from 164 to 216 (P<.001). This was due to a significant decrease in both longitudinal ($\theta_t$) and transverse ($\theta_L$) conduction velocity, although the ratio of anisotropy did not change (3.5 versus 3.6, P=.32). In contrast to the cycle length of VT, the refractory period at three pacing sites was only slightly prolonged from 97 to 106 milliseconds (P<.05). As a result, Org7797 considerably enlarged the excitable gap during VT from 67 to 110 milliseconds (P<.001). The ratio between the excitable gap and the refractory period increased from 0.68 to 1.03 (P<.05). During Org7797 administration, the threshold for stimulation was increased from 0.29±0.08 to 0.40±0.08 mA (P<.05). Heptanol increased the cycle length of VT from 166 to 228

<table>
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<th>Experiment</th>
<th>Control</th>
<th>Org7797 (0.5 μmol/L)</th>
<th>Heptanol (1.0 mmol/L)</th>
<th>ß-Sotalol (35 μmol/L)</th>
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CL indicates cycle length; DWR, sustained double-wave reentry; and NS, nonsustained.
milliseconds ($P<.001$). $\theta_9$ was affected more than $\theta_8$, resulting in a significant increase in the anisotropy ratio from 3.8 to 4.9 ($P<.05$). Because the refractory period increased less than the cycle length of VT, administration of heptanol resulted in a considerable prolongation of the excitable gap from 63 to 112 milliseconds ($P<.001$). The ratio between the refractory period and the excitable gap increased from 0.62 to 0.97 ($P<.05$). During heptanol, the threshold for stimulation was increased from $0.32 \pm 0.09$ to $0.39 \pm 0.11$ mA ($P<.05$).

Inducibility of Double-Wave Reentry During Org7797 and Heptanol Administration

Both Org7797 and heptanol considerably changed the susceptibility to acceleration of VT. In all 7 hearts, either the administration of Org7797 or heptanol enabled the induction of double-wave reentry (Table 1). Fig. 2 shows the mechanism of acceleration of VT after administration of Org7797. Whereas during control rapid pacing did not lead to acceleration of VT, during Org7797, sustained double-wave reentry was induced by entrainment with a pacing interval of 120 milliseconds. The left map shows the effects of Org7797 on the activation pattern during VT. The circulating wave traveled in a clockwise direction but compared with control conduction velocity was depressed in all segments of the circuit. In the segment between the LAD and the central obstacle at the outer edge of the ring, a local inhomogeneity in conduction occurred from the 60- to the 110-millisecond isochron over a distance of 4.5 mm. During the first stimuli, the normal pattern of entrainment was present (not shown). However, during $S_9$ (middle map), the paced antidromic wave was blocked ($t=49$ milliseconds) in the corridor between the LAD and the obstacle. Because of slow conduction, the orthodromic wave of $S_9$ did not arrive before $t=140$ milliseconds at the site where block had occurred during $S_{10}$ (right map). The 91 milliseconds that elapsed between antidromic block of $S_{10}$ and arrival of the previous orthodromic wave of $S_9$ was sufficient for recovery of excitability at the site of block, and double-wave reentry was initiated. Because of the short and only partially excitable gap during double-wave reentry, the revolution time of each of the two waves was prolonged to 236 milliseconds, resulting in a VT cycle length of 118 milliseconds.

In Fig 3, a similar example is given of acceleration of VT by entrainment after administration of heptanol. During control, VT had a cycle length of 153 milliseconds and was terminated by rapid pacing at an interval of 100 milliseconds (top electrogram). During heptanol administration, the cycle length of clockwise VT increased to 188 milliseconds (upper left map). Entrainment with an interval of 100 milliseconds now resulted in acceleration of VT from 188 to 115 milliseconds (lower electrogram). During the first entrained beats, the normal pattern of collision and reset of VT occurred (not shown). The maps show the changes in activation pattern associated with acceleration of VT. During $S_9$, conduction block of the antidromic wave occurred at $t=26$ milliseconds close to the site of pacing (upper right map). The orthodromic wave of $S_8$ could now proceed unopposed and collided with the antidromic wave of $S_{10}$ (lower left map). As a result, after cessation of pacing, the orthodromic waves of both $S_9$ and $S_{10}$ could continue to circulate around the central obstacle, leading to sustained double-wave reentry (lower right map).

In one experiment, heptanol was washed out after sustained double-wave reentry had been induced. During
heptanol administration, the double-wave VT had a cycle length of 142 milliseconds (Fig 4, left). After the infusion of heptanol was stopped, first the VT accelerated to 116 milliseconds (middle map). This was due to the reversibility of the uncoupling effect of heptanol, resulting in a restoration of the original conduction velocity. After about 3 minutes, suddenly the rate of tachycardia markedly decreased and the cycle length of VT abruptly increased from one beat to the next from 116 to 206 milliseconds. As can be seen from the activation maps, this was caused by the disappearance of one of the two circulating waves, converting the fast double-wave tachycardia into a slower single-wave reentry.

Termination of Double-Wave Reentry by D-Sotalol

In the 4 hearts in which during control VT could be accelerated, D-sotalol (35 μmol/L) was administered. The cycle length of VT increased only slightly from 205 to 217 milliseconds (P<.05). Both θr and θf tended to decrease slightly, but the ratio of anisotropy (θr/θf) was not changed (P=.59). The refractory period during VT was increased by 15%, from 116 to 133 milliseconds (P<.05). As a result, although the excitable gap shortened only slightly from 89 to 84 milliseconds (NS, P=.07), the ratio between the excitable gap and the refractory period decreased significantly from 0.76 to 0.63 (P<.05) (see Table 2).

The decrease in conduction velocity during VT by D-sotalol could not be explained by shortening of the excitable gap. This is illustrated in Fig 5. In this example, the cycle length of a clockwise VT had been slightly prolonged by D-sotalol from 198 to 207 milliseconds. During control, premature beats up to a coupling interval of 140 milliseconds were conducted without delay with the same revolution time around the ring as the VT cycle length of 198 milliseconds. During D-sotalol administration, premature beats up to a coupling interval of 165 milliseconds conducted with the same velocity as during VT with a revolution time of 207 milliseconds. This demonstrates that during D-sotalol, a large, fully excitable gap still was present during VT. Thus, the slowing of conduction.

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**Fig 3.** Electrograms at the top show termination of ventricular tachycardia (VT) by rapid pacing during control and acceleration of VT after administration of heptanol. The four maps show the transition from single-wave (upper left) to double-wave reentry (lower right). During S9 (upper right), antidromic block occurred close to the pacing site, resulting in two circulating orthodromic waves. Lower left map shows entrainment of double-wave reentry by S10. After cessation of pacing, sustained double-wave reentry with a cycle length of 116 milliseconds became apparent (lower right map). In the upper right and lower left maps, the moment of stimulation is taken as t=0. Activation times are given in milliseconds; isochronous lines are drawn at 10-millisecond intervals. Arrows indicate direction of wave fronts. Double bar indicates conduction block. LAD indicates left anterior descending coronary artery.
HEPTANOL → WASH-OUT

Double-Wave Reentry → Single-Wave Reentry

FIG 4. Conversion of double-wave reentry to single-wave tachycardia during washout of heptanol. The left map and the electrogram at the top show the activation of double-wave tachycardia with an interval of 142 milliseconds during heptanol. During washout, double-wave ventricular tachycardia (VT) first accelerated to 116 milliseconds (middle). Suddenly, after 3 minutes of washout, the fast VT spontaneously converted to a slower VT with an interval of 206 milliseconds, based on a single circulating wave around the obstacle (right). Activation times are given in milliseconds; isochrons are drawn at 10-millisecond intervals. Arrows indicate the direction of the circulating waves. Calibration bar=5 mV.

during VT cannot be explained by propagation of the circulating wave through partially refractory tissue. During d-sotalol, entrainment could still terminate VT in all hearts. However, the inducibility and stability of double-wave reentry was markedly affected by d-sotalol (Table 1). In 2 hearts, entrainment could still induce double-wave reentry, but the accelerated VT was no longer sustained and within a few seconds converted spontaneously to the original VT. In the other 2 hearts, d-sotalol completely prevented induc-
tion of double-wave reentry. Fig 6 gives an example of both responses. The upper two tracings show that during control, pacing at an interval of 95 milliseconds resulted in sustained acceleration of VT from 189 to 109 milliseconds. After d-sotalol was added, VT was slowed to 197 milliseconds and entrainment only resulted in nonsustained acceleration of VT to 115 milliseconds. The lower two tracings illustrate that after d-sotalol, double-wave reentry could no longer be induced.

In two hearts, infusion of d-sotalol was started after sustained double-wave reentry had been induced. First, d-sotalol gradually slowed the accelerated VT from 109±6 to 121±4 milliseconds until it was suddenly converted to single-wave reentry with a cycle length of 213±9 milliseconds. In Fig 7, three consecutive maps and the associated electrograms around the circuit are given during conversion of double-wave to single-wave reentry by d-sotalol. Before termination of double-wave reentry, the revolution time of the two circulating waves was 236 milliseconds, leading to a VT cycle length of 118 milliseconds (left map). Suddenly, one of the two circulating waves was blocked between electrodes C and D in the area of slow conduction between the LAD and the central obstacle (middle map). This resulted in a sudden prolongation of the VT cycle length from 118 to 219 milliseconds (right map). After the sudden disappearance of one of the two waves, the revolution time of the remaining wave decreased from 236 to 219 milliseconds. This increase in conduction velocity can be explained by the larger excitable gap during single-wave reentry. Obviously, during double-wave reentry, only a partially excitable gap existed between the two circulating waves, decreasing the conduction velocity of both wave fronts.

Importance of the Pacing Site for Induction of Double-Wave Reentry

In all 11 hearts, entrainment was performed at three different pacing sites around the circuit located at the base, the free wall, and the apex of the left ventricle. Both during control and during administration of heptanol, Org7797, and d-sotalol, VT could be terminated by conduction block of one of the paced orthodromic waves during entrainment. In 85% of all cases of termination of VT, the site of orthodromic block was located in the corridor between the LAD and the central obstacle. Previously, we have demonstrated that conduction block preferentially occurred in the segment of slow transverse conduction. During rapid pacing from each of the three sites, the paced orthodromic wave propagated through at least part of the segment of slow transverse conduction. Consequently, VT could be terminated from all sites around the circuit, and there was no preferential pacing site for termination of VT.

In all cases of induction of double-wave reentry, both during control and after administration of drugs, one of the paced antidromic wave fronts was blocked. Because conduction block occurred preferentially in the segment of slow conduction, antidromic block and double-wave reentry could only be induced by pacing distal to the segment of slow conduction. Thus, during clockwise VT, double-wave reentry could only be induced by pacing at the base, whereas during counterclockwise VT, initiation of double-wave reentry only occurred during entrainment at the apex.

Discussion

Antiarrhythmic Effects of Heptanol, Org7797, and d-Sotalol

Antiarrhythmic drugs can be effective either by terminating VT, slowing its rate, or by lowering the inducibility of VT. In our study, the experimental class Ic drug Org7797 and the uncoupling agent heptanol both slowed VT by about 35%, whereas d-sotalol only slightly slowed VT by 6%. Spinelli and Hoffman have shown that during atrial flutter, class I drugs were also more effective than class III drugs in slowing the rate. The slowing of conduction during VT by d-sotalol could not be explained by shortening of the excitable gap. The fact that early premature wave fronts could propagate around the circuit without any slowing of conduction strongly suggests that in our model of VT (also during administration of a class III drug), a fully excitable gap existed. In a previous study, Carmeliet showed that in guinea pig papillary muscle, sotalol reduced Vmax at concentrations above 100 μmol/L. In ventricular trabecular muscle, Nakaya et al found that 30 μmol/L sotalol reduced Vmax by 10%. We therefore assume that in our preparation, the slowing of conduction velocity by d-sotalol may have been due to a slight class I effect.

Both class I and class III drugs at low concentrations have been shown to be very successful in termination of experimental atrial flutter. In our experiments, neither heptanol, Org7797, nor d-sotalol were able to terminate VT. Application of premature stimuli under these conditions also failed to terminate VT. This indicates that in our model of reentrant VT, both during control and during antiarrhythmic drugs, a high safety factor for
DOUBLE-WAVE

BLOCK

SINGLE-WAVE

Fig 7. Conversion of double-wave to single-wave reentry by administration of d-sotalol (35 μmol/L). Three activation maps at the top show before, during, and after conversion. Electrograms A-M were recorded around the circuit as indicated in the middle map. Before termination, the cycle length of double-wave ventricular tachycardia was 118 milliseconds (left map). In the middle map, one of the two circulating waves was blocked between electrodes C and D in the corridor between the left anterior descending coronary artery (LAD) and the central obstacle. The remaining wave front continued to circulate with a cycle length of 219 milliseconds (right map). Activation times are given in milliseconds; isochron lines are drawn at 10-millisecond intervals. Arrows indicate direction of wave fronts. Double bar indicates conduction block. Calibration bar=5 mV.

Conduction still existed in every segment of the circuit. On the other hand, if a reentrant tachycardia can be terminated by antiarrhythmic drugs, this may implicate that at least in some part of the circuit, a low safety factor for conduction must exist.

Effects of Drugs on the Inducibility of Double-Wave Reentry

For the induction of double-wave reentry, the following three prerequisites must be fulfilled. First, one of
the stimulated antidromic wave fronts during entrainment must be blocked. Second, the dimensions of the circuit should be such that the orthodromic wave of the previous stimulus arrives late enough to allow recovery of excitability and reentry of the site of block. Third, the ratio between the excitabile gap and the refractory period should be large enough for double-wave reentry to become sustained. During control, acceleration of VT only occurred in the 4 hearts with the longest cycle length and the largest excitabile gap. In these cases the refractory period still exceeded the excitabile gap. However, during entrainment, a rate-dependent shortening of the refractory period must have increased the ratio between the excitabile gap and the refractory period above 1, thus providing enough space for a second wave to circulate. Because the revolution time of each circulating wave was longer than during single-wave reentry, only a partially excitabile gap was present during double-wave reentry.

Both Org7797 and heptanol decreased the conduction velocity more than they prolonged refractoriness. The resulting shortening of the wavelength is considered to be proarrhythmic because it promotes the occurrence of reentry.\textsuperscript{21,22} In this respect, D-sotalol was antiarrhythmic because it prolonged the wavelength by increasing the refractory period more than depressing the conduction velocity. This is in agreement with our present findings that Org7797 and heptanol both facilitated acceleration of VT, whereas D-sotalol prevented induction of sustained double-wave reentry. In addition, both administration of D-sotalol and washout of heptanol terminated double-wave reentry. The critical factor that determines whether a reentrant circuit can sustain two waves is the ratio between the excitabile gap and the refractory period. Both Org7797 and heptanol increased the excitabile gap to such extent that it equaled the refractory period. On the other hand, D-sotalol decreased the ratio between the excitabile gap and refractory period, and in 2 of 4 hearts, double-wave reentry was no longer inducible. In the other 2 hearts, double-wave reentry was no longer sustained. After cessation of pacing, the reduction in rate probably prolonged the refractory period to such an extent that the excitabile gap was closed and double-wave reentry could no longer be sustained.

Feasibility of Double-Wave Reentry in Functionally Determined Reentrant Circuits

Our results show that an anatomic reentrant pathway with a large excitabile gap is a suitable substrate for double-wave reentry. The question arises as to whether functionally determined reentry also can be accelerated by induction of a second circulating wavefront. As shown in the present study, double-wave reentry can only be induced when the ratio between the excitabile gap and the refractory period approaches 1. During functionally determined reentry, generally there is no or only a small partially excitabile gap.\textsuperscript{2,3,8-10,23,24} In uniform anisotropic myocardium, during functional reentry the excitabile gap was found to be 27\% of the VT interval, with a ratio between the excitabile gap and the refractory period of not more than 0.37.\textsuperscript{24} In an experimental model of canine myocardial infarction, several investigators have demonstrated that functional reentrant circuits in the epicardial border zone of the infarct can be reset and entrained, demonstrating the presence of an excitabile gap.\textsuperscript{2,3,8} In some of these circuits, part of the excitabile gap was fully excitabile because stimulated wavefronts propagated around the circuit with the same revolution time as the circulating wave during VT.\textsuperscript{2,8} The actual size of the excitabile gap was not determined but appeared to be not more than 25\% of the VT cycle length. On the other hand, Dillon et al\textsuperscript{8} recently observed an isolated case of double-wave reentry during functional VT after canine myocardial infarction; however, during our experiments on functional reentry,\textsuperscript{9,10,24} it has never been observed. Although it is uncertain to what extent our present data in an anatomic model of reentry can be extrapolated to functional models of reentry, it appears to be unlikely that double-wave reentry plays an important role in functionally determined tachycardia. However, if antiarrhythmic agents (class Ic drugs) enlarge the excitabile gap of functional reentry, the susceptibility to double-wave reentry may be enhanced.

Clinical Implications

The significance of double-wave reentry as a mechanism of acceleration of VT after myocardial infarction in patients, either in the presence or absence of antiarrhythmic drugs, is unclear. In a study on the mechanisms of acceleration of clinical VT, Brugada et al\textsuperscript{5} speculated that in 2 of 22 patients, the criteria for double-wave reentry might possibly have been fulfilled. However, systematic clinical studies on the inducibility of double-wave reentry at several pacing sites have not yet been performed.

Our present results indicate that the induction of double-wave reentry highly depends on the localization of the pacing site relative to the area of slow conduction. Therefore, the possibility of the reentrant substrate to accommodate two circulating waves may be seriously underestimated if only one pacing site is being used. In addition, one should be aware that antiarrhythmic drugs that widen the excitabile gap of a VT may enhance the susceptibility to acceleration of VT by double-wave reentry.

We would like to emphasize that the substrate for clinical VT after myocardial infarction is much more complex than our simple model of normal anisotropic myocardium.\textsuperscript{25-28} For this reason, extrapolation of our results to the clinical situation must be performed with caution. On the other hand, the present experimental findings may help to clarify the various possible proarrhythmic and antiarrhythmic actions of pharmacological agents.

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