Echo-Wave Termination of Ventricular Tachycardia
A Common Mechanism of Termination of Reentrant Arrhythmias by Various Pharmacological Interventions

Josep Brugada, MD; Lucas Boersma, MD; Hoshiar Abdollah, MD; Charles Kirchhof, MD; and Maurits Allessie, MD

Background. Based on epicardial mapping, different mechanisms of termination of reentrant ventricular tachycardia by various pharmacological interventions are described.

Methods and Results. In 40 Langendorff-perfused rabbit hearts, rings of anisotropic left ventricular epicardium were made by a cryoprobe. Sustained monomorphic ventricular tachycardia based on continuous circuit movement of the impulse around the ring was induced by programmed stimulation. Increasing doses of heptanol (n=10), potassium (n=10), tetrodotoxin (n=6), RP62719 (a new class III drug) (n=4), flecainide (n=5), and propafenone (n=5) were administered to terminate ventricular tachycardia. Epicardial mapping (248 points) was used to study the mechanism of termination of ventricular tachycardia. In 28 of 40 hearts, ventricular tachycardia terminated because the drugs produced complete conduction block of the impulse in a segment of the reentrant pathway. In the remaining 12 hearts (heptanol, n=2; potassium, n=3; tetrodotoxin, n=2; RP62719, n=2; flecainide, n=1; and propafenone, n=2), termination of ventricular tachycardia occurred by collision of the circulating impulse with a spontaneous antidromic wave front reflected within the circuit. This phenomenon occurred when the circulating impulse encountered an arc of functional conduction block that did not extend along the circumference of the ring. As a result, the impulse dissociated into a continuing orthodromic circulating wave and a returning antidromic echo-wave caused by microreentry within the ring.

Conclusions. Independent of their mechanisms of action, sodium channel blockers, electrical uncouplers, and class III drugs terminate reentrant ventricular tachycardia either by complete conduction block or by collision of the impulse with an echo-wave. (Circulation 1992;85:1879–1887)

Key Words • reentry • ventricular tachycardia • echo-wave • conduction block • sodium channel blockers

Propagation of the cardiac impulse can be modified by various pharmacological interventions. Sodium channel blockers like class I antiarrhythmic drugs and tetrodotoxin decrease conduction velocity by a depression of the amplitude and \( V_{\text{max}} \) of phase 0 of the action potential.\(^1,^2\) Electrical uncouplers like heptanol mainly decrease conduction velocity by increasing the intercellular resistance.\(^3\) High extracellular potassium decreases conduction velocity by depolarizing the cells and therefore decreasing the number of sodium channels available for the generation of phase 0 of the action potential.\(^4\) Class III drugs prolong the duration of the action potential and the refractory period and may slow down conduction if the impulse propagates through partially refractory tissue.\(^5\) At adequate dosage, all these agents can depress impulse propagation to such an extent that reentrant arrhythmias are terminated.\(^6–^8\) In this study we show that independent of their mechanisms of action, termination of reentrant ventricular tachycardia by drugs results either from complete conduction block of the electrical impulse in part of the ring or by collision of the circulating impulse with a spontaneous antidromic echo-wave resulting from microreentry within the reentrant pathway.

Methods

A previously reported experimental model of reentrant ventricular tachycardia around a ring of epicardium in Langendorff-perfused rabbit hearts was used in this study.\(^7^9,^10\) Forty Flemish rabbits of both sexes weighing between 3.3 and 4.8 kg were used. Briefly, the experimental model consisted of a ring of left ventricular epicardium about 1 mm thick obtained by an endocardial cryoprobe while the right ventricle and the interventricular septum are completely destroyed. In this experimental model, sustained monomorphic ventricular tachycardia around the ring...
can be reproducibly induced by programmed electrical stimulation.\textsuperscript{7,9,10}

**Recording and Stimulation**

High-resolution mapping of the epicardial excitation pattern was performed using a spoon-shaped electrode containing 248 individual silver electrodes (diameter, 0.3 mm) regularly spaced at 2.25 mm. With this mapping electrode, 248 unipolar electrograms were simultaneously and continuously recorded from the left ventricular epicardium. The mapping system used for acquisition, storage, and data analysis has been described previously.\textsuperscript{11}

**Experimental Protocol**

During sustained reentrant ventricular tachycardia, the following substances were administered until tachycardia terminated: 1) heptanol in steps of 1 mmol/l at 30-minute intervals (n=10), 2) potassium in steps of 2 mmol/l at 5-minute intervals (n=10), 3) tetrodotoxin in steps of 5 mmol/l at 5-minute intervals (n=6), 4) RP62719 as a single dose of 0.03 mmol/l (n=4), 5) flecainide (Tambocor\textsuperscript{®}) in steps of 1 mg/l at 15-minute intervals (n=5), and 6) propafenone (Rythmonorm\textsuperscript{®}) in steps of 1 mg/l at 15-minute intervals (n=5). The drugs were infused through a cannula close to the aorta of the Langendorff-perfused hearts. (RP62719 is an experimental class III drug\textsuperscript{12} provided by Rhône-Poulenc Santé.)

**Statistical Analysis**

Statistical analysis was performed using the paired Student's \(t\) test to evaluate drug effects compared with control. Comparison between different groups was performed using the Mann-Whitney rank sum test. A value of \(p<0.05\) was taken as statistically significant.

**Results**

During a control period of 30 minutes, ventricular tachycardia cycle length was extremely regular with a spontaneous variability of \(\pm 2\) msec. Spontaneous termination of the reentrant rhythm was never observed during this control period. In Table 1, the cycle lengths of ventricular tachycardias are given both during control and before termination by the different drugs. During control, the cycle length was computed as the mean value of 30 consecutive cycles, whereas the cycle length before termination represents the last complete revolution time around the ring in the orthodromic direction before termination. With the exception of the class III drug RP62719 compared with control, all drugs significantly prolonged the tachycardia cycle length before termination.

Termination of tachycardia by sudden complete conduction block of the circulating impulse in a segment of the ring occurred in 28 of 40 hearts. Complete conduction block was defined as the occurrence of a sudden stop in the propagation of the impulse around the ring not preceded by a change in the circulating pathway or in the activation pattern and resulting in termination of the reentrant rhythm. In Figure 1, an example of termination by complete conduction block is given during administration of 7 mg/l flecainide. During control, the tachycardia propagated in a clockwise direction around the ring with a cycle length of 199 msec (Figure 1, upper panel). During infusion of increasing dosages of flecainide, conduction velocity of the circulating impulse was progressively depressed, therefore causing a gradual prolongation of the tachycardia cycle length to 575 msec (Figure 1, lower panel). Termination occurred because of sudden conduction block of the circulating impulse in the lower left segment of the ring between electrodes 14 and 15.

In 12 of 40 hearts, termination of tachycardia occurred by collision of the circulating impulse with a spontaneous antidromic wave being reflected in the ring. This phenomenon is illustrated in Figure 2. In this example the control tachycardia propagated clockwise around the ring at a cycle length of 130 msec. During administration of 30 mmol/l of tetrodotoxin, tachycardia cycle length prolonged to 672 msec (Figure 2, right panel). Before termination (map A) the main wave still continued its circular course, but in part of the ring, conduction had become dissociated, causing the impulse to travel in an opposite direction from electrode 9 to 6. However, this antidromic wave front was blocked at electrodes 5 and 4 (double bars), and the tachycardia continued. During the last beat of the tachycardia (Figure 2, maps B and C), the antidromic wave front suddenly succeeded in propagating farther in an antidromic direction and collided with the circulating orthodromic wave at electrode 1. This resulted in sudden termination of the tachycardia. In Figure 3, the complete activation maps during this phenomenon are shown. During control (Figure 3, upper left panel) in different segments of the ring, conduction velocity of the circulating impulse varied between 24 and 64 cm/sec, depending on the direction of propagation relative to the epicardial fiber orientation.\textsuperscript{10} Panels A-C of Figure 3 represent the last two beats of the tachycar-

<table>
<thead>
<tr>
<th>No. of hearts</th>
<th>Ventricular tachycardia cycle length during control (msec)</th>
<th>Ventricular tachycardia cycle length before termination (msec)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heptanol</td>
<td>10</td>
<td>144±13</td>
<td>446±120</td>
</tr>
<tr>
<td>Potassium</td>
<td>10</td>
<td>142±13</td>
<td>493±341</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>6</td>
<td>167±17</td>
<td>793±122</td>
</tr>
<tr>
<td>RP62719</td>
<td>4</td>
<td>145±15</td>
<td>164±28</td>
</tr>
<tr>
<td>Flecainide</td>
<td>5</td>
<td>171±17</td>
<td>721±127</td>
</tr>
<tr>
<td>Propafenone</td>
<td>5</td>
<td>142±13</td>
<td>520±346</td>
</tr>
</tbody>
</table>

Values are mean±SD.

### Table 1. Cycle Length of Ventricular Tachycardia During Control and Before Termination
Figure 1. Termination of tachycardia by complete conduction block of the circulating impulse. Eighteen electrograms around the obstacle are shown together with the total epicardial activation maps both during control and termination of tachycardia during administration of flecainide (7 mg/l). During control, the impulse propagated in a clockwise direction around the obstacle (empty area in the center of the map) with a cycle length of 199 msec. During administration of flecainide, the tachycardia markedly slowed down to a cycle length of 575 msec. Suddenly, propagation of impulse was interrupted between electrodes 14 and 15 (double bars), and tachycardia was terminated. Location of the electrograms around the ring is shown by the encircled numbers in the upper map. Numbers in the map indicate local activation times in msec. Isochrones are drawn at 10-msec intervals. LAD, left anterior descending coronary artery.

dia; the respective time windows of the maps are indicated by the dotted vertical lines in Figure 2. The significant slowing of the tachycardia by tetrodotoxin to a cycle length of 672 msec was caused by a marked depression of the conduction velocity in all segments of the ring, which now varied between 5 and 15 cm/sec. In addition, in the upper right segment, a line of functional conduction block was present, extending from the base to the mid part of the free wall of the left ventricle (thick line). Functional conduction block was defined as the occurrence of a change in the pattern of activation in a segment of the ring resulting in an activation time difference between two contiguous electrodes of more than 50 msec and in the recording of double potentials across the line of block. In Figure 3, the line of block dissociated the upper right quadrant of the ring in an inner pathway where the impulse continued to circulate around the perimeter of the central obstacle and an outer pathway where the impulse propagated in the opposite direction after having turned around the lower end of the line of block. However, the time difference of 200 msec between activation of the tissue proximal and distal to the line of block (activation times [t], 137 and 337 msec, respectively) was not long enough for the cells proximal to the arc of block to recover their excitability, and bidirectional block occurred. During the next cycle (Figure 3B), the line of functional block was extended into the direction of the apex by about 7 mm, and the
longer return pathway resulted in a maximal time difference between the orthodromic and the antidromic waves of 275 msec (t=149 and 424 msec, respectively). As can be seen from Figure 3C, this longer time delay now was sufficient for the myocardium proximal to the line of block to restore its excitability, resulting in reentry by the antidromic wave. As a result, two waves propagated through the ring in opposite directions, one in a clockwise direction (the original circulating wave) and another in a counterclockwise direction (the spontaneous antidromic echo-wave). Collision of these opposite wave fronts at t=667 msec at the upper left part of the ring extinguished both waves and terminated the tachycardia.

In Table 2, the characteristics of termination by complete conduction block and collision with an antidromic echo-wave are given. With all drugs, both modes of termination of tachycardia were observed. Echo-wave termination occurred in 12 of 40 cases: two of 10 with heptanol, three of 10 with potassium, two of six with tetrodotoxin, two of four with RP62719, one of five with flecaainide, and two of five with propafenone. For either drug, no statistically significant difference in cycle length existed between tachycardias that terminated by complete conduction block or by collision with reflecting echo-wave. Also, no differences were found in the concentration of the drug at which tachycardia terminated by one or the other mechanism.

In Figure 4, echo-wave termination of tachycardia is shown during administration of heptanol. During control, the tachycardia propagated in a counterclockwise direction with a cycle length of 133 msec. During administration of 3 mmol/l of heptanol, tachycardia terminated at a cycle length of 408 msec. Crowding of isochrones preferentially occurred in the corridor between the left anterior descending coronary artery (LAD) and the obstacle (Figure 4A). In this segment of the ring where the circulating impulse conducted perpendicular to the epicardial fiber orientation, several arcs of conduction block were seen. However, none of these arcs of block extended along the whole width of the ring, and the circulating impulse continued to propagate in a zig-zag fashion through this area. The largest local time difference in activation proximal and distal to a line of block was 101 msec (t=117 and 218 msec). This was not enough for recovery of excitability of the cells proximal to the block. However, during the next beat (Figure 4B), conduction around the arc of transverse block was further depressed, leading to a local phase difference in activation of 125 msec (t=121 and 246 msec). This time delay obviously was long enough for the cells proximal to the arc of block to recover their excitability, and reentry occurred (Figure 4C). As a result, two impulses now propagated through the ring, one in its normal counterclockwise direction and the other in a clockwise direction. Collision of both wave fronts close to the apex resulted in termination of the tachycardia at t=478 msec.

In Figure 5, an example of echo-wave termination by administration of a class III drug (RP62719) is shown. During control (Figure 5, upper left panel), the tachycardia propagated in a clockwise direction around the obstacle with a cycle length of 160 msec. During administration of 0.03 μmol/l of RP62719, tachycardia terminated. Two cycles before termination, the cycle length was 206 msec (Figure 5A). An arc of conduction block was present near the apex, dissociating the impulse in a faster propagating wave in the inner part of the ring. During the next cycle (Figure 5B), a long arc of conduction block was present in the lower right segment of

**Figure 2.** Termination of tachycardia by collision of the circulating impulse with an antidromic echo-wave. Twenty-one electrograms around the obstacle are shown during control and termination of tachycardia during administration of 30 μmol/l tetrodotoxin (TTX). Location of the electrograms around the ring is indicated on the activation map of Figure 3. During control, the impulse propagated clockwise at a regular cycle length of 130 msec. During TTX, the cycle length was prolonged to 672 msec. Before termination, the impulse became dissociated in part of the ring and travelled in both orthodromic and antidromic directions between electrograms 9 and 6 (map A). During the last beat of the tachycardia (maps B and C), the small antidromic wave front was no longer blocked at electrode 6 but continued its antidromic course to collide with the circulating impulse at electrode 1. This resulted in sudden termination of the tachycardia.
the ring, and the impulse now continued its circular course through the inner pathway around the obstacle. Starting at t=209 msec, the outer part of this segment of the ring was activated in a counterclockwise direction by an offspring of the circulating wave turning around the lower end of the line of block. After reentry of the ring by this antidromic wave front, the two opposite wave fronts collided, resulting in termination of the tachycardia at t=305 msec (Figure 5C).

All of these examples illustrate that the basic mechanism of termination of ventricular tachycardia by a spontaneous antidromic echo-wave was the same independent of the drug used. However, some differences should be noted. In all cases except during administration of the class III drug, a marked slowing of conduc-

FIGURE 3. Activation maps during control and echo-wave termination of tachycardia shown in Figure 2. During control (upper left panel), the impulse propagated in a clockwise direction around the obstacle with a cycle length of 130 msec. During administration of 30 μmol/l tetrodotoxin (TTX), the cycle length of ventricular tachycardia was prolonged to 672 msec (panel A). Termination of ventricular tachycardia (VT) (panels B and C) was caused by antidromic echo-wave that collided with the orthodromic circulating wave. Encircled numbers in the upper left map indicate the location of the electrograms shown in Figure 2. Numbers indicate local activation times in msec. Isochrones are drawn at 10-msec intervals. The time windows represented by maps A, B, and C are indicated by vertical dotted lines in Figure 2. LAD, left anterior descending coronary artery.
cases in which echo-waves appeared during administration of a class III drug, the location of the arcs of block changed from beat to beat. Together with the lack of depression of conduction velocity around the ring, this suggests that the main cause of conduction block during administration of a class III drug was a prolongation of the local refractory period. We measured the local refractory period by introducing an extrastimulus during ventricular tachycardia at progressively shorter coupling intervals. The shortest coupling interval still activating the ventricle and resetting the tachycardia was considered the local refractory period. The difference between the cycle length of the tachycardia and the refractory period was considered the excitable gap of the ventricular tachycardia at the site of stimulation. The refractory period prolonged from 110±11 msec during control to 160±27 msec before termination during administration of RP62719. The excitable gap of the tachycardia decreased from 38±10 msec during control to 12±7 msec before termination.

### Discussion

The rationale of treatment of reentrant arrhythmias with drugs that depress conduction or prolong the refractory period is to interrupt the circulating impulse by creating conduction block in part of the circuit. In the present series of experiments, the main effect of administration of sodium channel blockers was to slow down the rate of ventricular tachycardia. Termination of ventricular tachycardia did not occur until high concentrations of the drugs prolonged the cycle length of the ventricular tachycardia to more than 250%. Also, application of heptanol, which increases the coupling resistance between the myocardial cells, terminated ventricular tachycardia only after the cycle length of ventricular tachycardia was prolonged to more than 200%. Obviously, the safety factor for conduction was rather high in all parts of the circuit, and ventricular tachycardia was terminated only when the active or passive membrane properties were depressed close to total inexcitability of the myocardium. This was true despite the presence of a considerable degree of anisotropy in the ring. As previously demonstrated using the same experimental model, because of differences in the angle of propagation relative to the fiber orientation, during control, longitudinal conduction velocity was about three times faster than transverse propagation. In the majority of the cases, ventricular tachycardia was terminated by complete conduction block of the circulating impulse. In 12 of 40 cases, arcs of conduction block developed, which did not extend along the whole width of the ring. If the conditions were appropriate, microreentry around these arcs of functional conduction block initiated an antidromic echo-wave that terminated ventricular tachycardia by collision with the orthodromic circulating wave front. The location of the arcs of conduction block from which the antidromic echo-waves originated depended on the preferential site of action of the drugs. It has been previously shown that drugs that depress sodium channels preferentially depress the fast conducting limb of the circuit and that conduction block occurred in segments of the circuit where conduction was parallel to the fiber orientation. It has also been shown that electrical uncouplers like heptanol preferentially affect slow transverse conduction leading to arcs of conduction block in part of the circuit where the impulse conducts perpendicular to the fiber axis.

Termination of atrial flutter by collision with an antidromic impulse was observed by Spinelli and Hoffman during administration of D-sotalol. They postulated that the antidromic impulse originated either from failure of the lateral boundaries of the circus path or from reflection within the circuitous pathway. In the present study, high-resolution epicardial mapping showed that the antidromic impulse originated from microreentry within the macroreentrant pathway. As for any other type of reentry, unidirectional conduction block and slow conduction over an alternative pathway were prerequisites for the echo-wave to occur. The balance between the size of the reentrant pathway and the local wavelength of the impulse determined initiation of the antidromic wave. During administration of heptanol, which dramatically depresses transverse conduction velocity in this model, one can assume that the wavelength in the transverse segment of the ring is markedly shortened, and relatively short arcs of conduction block may lead to the initiation of antidromic echo-waves. However, during administration of class III drugs, the prolongation of the refractory period together with the lack of significant impairment of conduction velocity might result in a prolongation of the wavelength. Under these conditions, an antidromic echo-wave only may occur around relatively long arcs of functional conduction block.

During echo-wave termination, the changes in time and direction of activation of part of the circuit might lead to a different sequence of activation of the ventricles. If, depending on the exit point to the ventricles, a considerable portion of the ventricles is activated by the

### Table 2. Mechanisms of Termination of Ventricular Tachycardia

<table>
<thead>
<tr>
<th></th>
<th>Complete conduction block</th>
<th>Echo-wave termination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of hearts</td>
<td>CL (msec)</td>
</tr>
<tr>
<td>Heptanol</td>
<td>8</td>
<td>449±132</td>
</tr>
<tr>
<td>Potassium</td>
<td>7</td>
<td>559±358</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>4</td>
<td>786±48</td>
</tr>
<tr>
<td>RP62719</td>
<td>2</td>
<td>152±2</td>
</tr>
<tr>
<td>Flecaainide</td>
<td>4</td>
<td>709±124</td>
</tr>
<tr>
<td>Propafenone</td>
<td>3</td>
<td>669±347</td>
</tr>
</tbody>
</table>

CL, cycle length of ventricular tachycardia before termination (mean±SD); Conc [ ], concentration of drugs at which ventricular tachycardia terminated (expressed in mmol/l for heptanol and potassium, μmol/l for tetrodotoxin and RP62719, and mg/l for flecaainide and propafenone).
antidromic echo-wave, the QRS complex of the last beat will have a different configuration. Callans and Marchlinski16 studied the QRS complex morphology during spontaneous termination of 55 episodes of ventricular tachycardia in 28 patients with coronary artery disease. In 44 cases, termination occurred during antiarrhythmic therapy. In 7% of the cases, termination of tachycardia was associated with a change in QRS morphology. Obviously, our experimental model is an oversimplification of the pathophysiological substrate in patients with coronary artery disease, and extrapolation of the mechanisms of termination of reentrant rhythms to the clinical situation must be done with great care. Clinical studies are needed to clarify whether the changes in QRS complex morphology upon termination of clinical ventricular tachycardias might be indicative in some cases for echo-wave termination.

**Summary**

Two different mechanisms of termination of reentrant ventricular tachycardia were observed during dif-
different pharmacological interventions and independently of their mode of action: 1) complete conduction block of the circulating impulse in a segment of the ring or 2) collision of the ongoing orthodromic impulse with a spontaneous antidromic echo-wave resulting from microreentry within a macroreentrant circuit. These observations may be of interest for understanding the mechanisms of action of different antiarrhythmic agents during reentrant arrhythmias.

Acknowledgment

RP62719 is an experimental class III drug provided by Rhône-Poulenc Santé.

References
Echo-wave termination of ventricular tachycardia. A common mechanism of termination of reentrant arrhythmias by various pharmacological interventions.

J Brugada, L Boersma, H Abdollah, C Kirchhof and M Allessie

_Circulation_. 1992;85:1879-1887
doi: 10.1161/01.CIR.85.5.1879

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/85/5/1879

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/