The Mechanism of Termination of Reentrant Activity in Ventricular Fibrillation

Yong-Mei Cha, Ulrika Birgersdotter-Green, Paul L. Wolf, Barry B. Peters, Peng-Sheng Chen

**Abstract** The reentrant wave fronts in ventricular fibrillation (VF) have only a limited life span. The mechanisms by which these reentrant wave fronts terminate are unknown. We performed computerized mapping studies in six open-chest dogs before and after right ventricular subendocardial ablation with Lugol's solution. Recordings were made with 56 bipolar electrodes separated by 3 mm. Baseline pacing was performed on the right side of the tissue to create parallel activation wave fronts. A premature 50-V shock of either anodal or cathodal polarity was given to a bar electrode on the upper edge of the tissue. Counterclockwise reentrant wave fronts and VF were induced both before (60 episodes) and after (57 episodes) subendocardial ablation with either anodal or cathodal shocks. Among these reentrant wave fronts, 8 episodes before and 10 episodes after ablation had over 10 rotations (P=NS). The reentrant wave fronts in other episodes terminated with an average of 3.2±1.9 rotations before and 3.1±1.8 rotations after the ablation (P=NS). The reentrant wave-front cycle length was 118±19 milliseconds before and 124±20 milliseconds after ablation (P=.001). Conduction block occurred when the wave front was traveling across the myocardial fibers. When conduction was blocked in these episodes, the leading edge of the reentrant wave front encountered tissue that had been excited within the past 58±12 milliseconds (range, 28 to 77 milliseconds), which corresponded to 47±12% of the preceding VF cycle length. This period was significantly shorter than the recovery period in the same region that had allowed conduction (91±19 milliseconds; range, 48 to 137 milliseconds), which corresponded to 72±18% of the preceding VF cycle length (P<.001). In nine episodes, reentrant wave-front activity terminated when wave fronts that had originated from outside the mapped tissue interfered with the reentrant pathways. Conclusions are as follows: (1) The refractory period of fibrillating ventricular muscle ranges from 48 to 77 milliseconds. Because the refractory period is much shorter than the VF cycle length, a large excitable gap is present in the reentrant circuit. The presence of a large excitable gap contributes to reentrant wave-front termination. (2) Myocardial fiber orientation is an important determinant of the site of conduction block. (3) Although subendocardial ablation slowed the wave-front propagation, it did not prevent the generation and the maintenance of reentry and VF. (Circ Res. 1994;74:495-506.)

**Key Words** • excitable gap • Purkinje fibers • refractory period • polarity

Recently, it has been demonstrated that reentrant activities are present during ventricular fibrillation (VF) in normal healthy canine ventricles.1-3 The presence of reentrant activities has also been demonstrated in infarcted canine ventricles,4-5 in isolated6-8 and perfused9 ventricular tissue, and with computer simulation.10,11 When reentrant wave fronts are induced in isolated ventricular tissue, they are often sustained.6-8 However, during VF in the in situ normal ventricles, the reentrant wave fronts have a limited life span, lasting only 1.36 seconds or 9.6 cycles, before termination occurs.1 Because previous studies in the normal canine ventricles1,2 focused on the phenomena associated with the initiation of reentrant wave fronts, the mechanisms by which the reentrant wave fronts terminate in the normal ventricles are unclear. One possible mechanism could be related to the fact that, in the intact ventricles during VF, multiple reentrant wave fronts may be present at the same time. The wave fronts may thus compete and interfere with each other and result in the termination of reentrant excitation. If this is the case, then an excitable gap must be present in the reentrant wave fronts. A second possible mechanism could be related to the fact that Purkinje fibers are present in the intact ventricles but not in the isolated epicardial tissue. Because of the presence of the Purkinje fiber network, intact ventricles possess a higher degree of structural and functional inhomogeneity, which may result in a higher likelihood of wave-front aberration and eventual termination. The same structural inhomogeneity that is induced by Purkinje fibers could also contribute to the generation of new reentrant wave fronts, hence complicating the epicardial activation patterns. If this is the case, then chemical ablation of the subendocardial tissue should significantly alter the reentrant wave-front life span and the patterns of activation in the intact ventricles.

The purpose of the present study was to use computerized epicardial mapping techniques to examine the initiation and the termination of reentrant wave fronts induced by single premature stimulation. The reentrant wave fronts were analyzed to test the following hypotheses: (1) An excitable gap is present during VF. (2) Chemical subendocardial ablation significantly alters the patterns of activation and the life span of the reentrant wave fronts.

**Materials and Methods**

**Surgical Preparation**

The surgical procedures were performed in accordance with institutional guidelines. Six adult mongrel dogs were anesthetized with 25 to 35 mg/kg sodium pentobarbital, intubated, and ventilated with room air by a respirator (Harvard Apparatus, Millis, Mass). An arterial line was inserted into the right
Feemoral artery to continuously monitor systemic blood pressure. Blood was drawn to determine the pH, P02, PC02, base excess, and bicarbonate concentrations. Normal metabolic status was maintained throughout the study by correcting any abnormal values. A venous line was inserted into the femoral vein to infuse supplemental doses of pentobarbital. Rectal temperature was monitored and maintained at =36°C to 37°C by heating the table with warm circulating water.

The chest was opened through a medial sternotomy, and the heart was suspended in a pericardial cradle. Recordings were made with a plaque electrode array containing seven columns and eight rows of bipolar electrodes (Fig 1), with an interelectrode distance of 3 mm and an interpolar distance of 1 mm. The electrode array was sutured to the epicardial surface of the right ventricular anterior wall, 1 cm below the pulmonary conus. The recording electrodes were connected to a 64-channel computerized mapping system (Bard electrophysiology, Tewksbury, Mass). The bipolar electrogram was filtered from 30 to 300 Hz and digitized at 1000/s with 12-bit accuracy.

The surface electrocardiogram leads I, II, III, aVR, aVL, aVF, and V6 and 56 channels of the bipolar epicardial electrogram were recorded simultaneously. The surface ECG and eight selected epicardial electrogram signals were also continuously displayed on a monitor throughout the study. Baseline cathodal pacing using a 10-mA stimulus was performed simultaneously from eight pacing wires, 3 mm apart, on the right edge of a recording plaque, with the chest wall being used as an anode to create a parallel activation wave front. After 11 S, stimuli at a cycle length of 300 milliseconds, a second channel of the programmable stimulator was used to deliver a premature stimulus (S1) to a high voltage stimulator (HVS-02, Ventritex, Sunnyvale, Calif). The S2 was used as an external signal to trigger the immediate delivery from the HVS-02 of a 6-millisecond 50-V truncated exponential shock to a copper bar electrode on the upper edge of the plaque electrode array (Fig 1). Both anodal and cathodal shocks were used, with the chest wall connected to the opposite pole. The sequence of delivering the anodal and the cathodal shocks in each dog was randomized. Two patch defibrillation electrodes with an active surface area of 13.5 cm2 (CPI, St Paul, Minn) were sutured to the right and left ventricular epicardium, distant from the recording electrode array, to deliver rescue shocks within 10 seconds after the induction of VF.

**Stimulation Protocol**

The first S1-S2 interval was shorter than the effective refractory period of the ventricles, usually <130 milliseconds. If VF was not induced, the S1-S2 interval was increased in 10-millisecond steps to scan the vulnerable period of the ventricles until VF was induced. The activation patterns at the onset of VF were analyzed. If reentrant wave fronts were observed, the same S1-S2 interval was used to induce an additional four VF episodes. The polarity of the shock was then reversed, and the same protocol was repeated. There was a 4-minute interval between each fibrillation/defibrillation episode.

**Chemical Subendocardial Ablation**

After the baseline data were obtained, the subendocardium of the right ventricle was ablated with Lugo's solution according to a method previously described in detail. Briefly, umbilical tapes were threaded around the venae cavae and the pulmonary artery in preparation for inflow and outflow occlusion. A catheter was inserted via the right atrial appendage into the right ventricular cavity. The umbilical tapes around the venae cavae and the pulmonary artery were tightened, and the right ventricular cavity was emptied by syringe. Lugo's solution (20 to 30 mL) was injected into the right ventricular chamber and maintained for 10 to 20 seconds. Right bundle branch block always occurred immediately after the injection of the Lugol's solution. Warm normal saline was then used to flush the same chamber multiple times to remove the Lugol's solution. The occlusion was then released, and the dog was allowed to recover for 30 minutes or until the blood pressure and the heart rate returned to normal. The total duration of the inflow and outflow occlusions was approximately 2 minutes. The same stimulation protocol was then repeated.

**Tissue Examination**

At the end of the study, the dogs were killed by an overdose of pentobarbital. The electrode array was removed, and the tissue underneath it was excised from the rest of the heart. The tissue was then fixed in a 10% buffered formalin solution. A horizontal section was first obtained 1 mm from the epicardium and was stained with hematoxylin and eosin. A photograph was taken, and the angle between the fiber orientation and the lower edge of the recording electrode array was determined on the basis of these photographs. Multiple transmural sections were taken from the entire block, including the upper, middle, and lower parts of the block. These samples, which were representative of the entire block, were stained with hematoxylin and eosin to document that effective subendocardial ablation by the Lugol's solution had occurred.

**Terminology**

The term "total activation time" is defined as the difference between the time of the earliest activation and the time of the latest activation on the isochronal map. Because the subendocardial layer is responsible for the rapid spread of excitation, effective subendocardial ablation is expected to increase the total activation time of the right ventricular epicardium. The total activation time in the present study could not be used to measure the conduction velocity between two epicardial points because of the possible transmural spread of excitation wave fronts. The total activation time was calculated for a VF activation only if a single large wave front was present in the entire mapped area.

**Data Analysis**

The recordings from each channel were displayed on a computer terminal. Baseline sinus activation and the patterns of activation after the S1 pacing were determined. All VF episodes were analyzed to determine the presence or absence of reentrant wave fronts on the epicardial surface at the recording site. If present, the reentrant wave front activation was analyzed either until it terminated or when 10 consecutive reentrant wave-front cycles were analyzed. The activation recorded by the bipolar electrodes might be monophasic, biphasic, or multiphasic. For the biphasic and the multiphasic
wave forms, the maximal slope of the activation complex was selected by the computer to be the time of activation, and only one activation time was assigned to the entire complex if no isoelectric period was present within the complex. Each activation complex was then inspected, and manual editing was performed. If the activation complexes were monophasic with a single maximum or minimum, the times of activation were reassigned to be at the peak of the maximal or minimal deflection.\(^5\) For complexes that were separated by an isoelectric period, multiple activation times were selected. This applied even to very small activation complexes. Thus, some of the times selected might not represent a propagated and a local response, and some channels had more activation times assigned than did other channels. In the present study, if two activations were within 50 milliseconds of each other, the one that was larger and had a greater dV/dt was included in the isochronal map.

Sometimes, the mismatch between the number of activations registered by neighboring channels was not due to the presence of multiple activations within 50 milliseconds of each other but was due to conduction block, which resulted in no activation in part of the mapped tissue. In this situation, “missing” markers were assigned to the channels with fewer activations selected, and the isochronal lines were not drawn in those electrodes. In the figures, these areas were represented by hatched lines.

In addition to isochronal lines, a thick line was also drawn between electrodes. These thick lines have the following two functions: The first is to indicate slow conduction or conduction block. A thick line was drawn if activation times between neighboring electrodes differed by >30 milliseconds. This interval between adjacent electrodes would represent a conduction velocity of <0.1 mm/ms, which was the minimal reported conduction velocity in the normal canine ventricle.\(^{13,16,17}\) However, we could not completely rule out that extraordinarily slow conduction had occurred in that area. The second function of the thick line was to serve as a frame line. Because the reentrant activation continues through multiple activations, it was not possible to show the continuous activations in one map. Therefore, thick lines were used to indicate that the activation shown in this map was not the end of the wave front but was a part of the continuous reentrant activity that would propagate into the next isochronal map.

All statistical analyses were performed using SYSTAT.\(^{18}\) The results were expressed as the mean±SD. Fisher’s exact test was used to compare the probability of reentrant wave fronts to continue for >10 rotations and to terminate by abrupt conduction block, before and after the subendocardial ablation. Nonpaired Student’s t tests were used to compare the means of reentrant wave-front cycle length and reentrant wave-front life span before and after chemical subendocardial ablation, between the means of reentrant wave-front cycle length induced with anodal and cathodal S1 shocks, between the recovery period preceding blocked wave fronts and the recovery period preceding conducted wave fronts, and between the means of total activation time in sinus rhythm and in single large activations during VF. Multivariate linear regression analysis was used to analyze the influence of the subendocardial ablation and the immediate preceding cycle length (the “pause” since previous activation) on the total activation time of the large wave fronts. The null hypothesis was rejected for values of P≤0.05.

Results

The dogs weighed 20±5 kg. The hearts weighed 179±45 g. The myocardial fiber orientation averaged 34.2±9.7°, with a range of 20° to 45°. The anodal and the cathodal shocks were each used to induce 5 episodes of VF before subendocardial ablation and 5 episodes of VF after subendocardial ablation. Thus, a total of 20 episodes of VF were mapped in each dog, and a total of 120 episodes of VF were mapped in the study. The S1–S2 intervals used to induce VF varied from 130 to 180 milliseconds. Counterclockwise reentrant wave fronts before and after ablation were observed in 117 episodes. The earliest activation observed was either at the lower A column recording sites (42 VF episodes) or at the lower B through E column recording sites (75 VF episodes).

Reentrant Wave-Front Termination

Among the 117 episodes of VF in which reentrant wave fronts were observed, the reentrant wave fronts of 18 episodes continued for over 10 cycles. In 47 episodes, the reentrant wave fronts drifted outside the mapped region, and in 6 episodes, only one reentrant cycle was observed. In the remaining 46 episodes, the activation patterns in 17 episodes were characterized by an abrupt conduction block within the reentrant wave front itself, resulting in termination. In 9 of the 46 episodes, competition with wave fronts from outside the mapped region was observed. These outside wave fronts interfered with the reentrant pathway and resulted in reentrant wave-front termination. In 20 of the 46 episodes, the reentrant wave fronts became unstable and changed to a different activation pattern before a conduction block occurred.

Termination by Conduction Block Within the Reentrant Wave Front

The 17 blocked reentrant wave fronts had 31 blocked recording electrode sites, including 17 sites before and 14 sites after Lugol’s ablation. Fig 2 shows that, after a 50-V anodal shock, a reentrant wave front was induced and the wave front rotated in a counterclockwise direction. The patterns of activation are compatible with the spiral-wave activities observed in vitro.\(^6-8\) The thick line in the middle of the isochronal map, which was drawn to separate the neighboring electrodes that registered activations >30 milliseconds between each other, has a shape that appears to be compatible with the linear core of spiral-wave vortices that have been observed in computer simulation studies.\(^19\) The reentrant wave front continued for eight cycles and then abruptly terminated. The hatched area in Fig 2E indicates that the wave front did not propagate to the right lower corner of the mapped tissue. The ninth activation invaded the mapped tissue from the left upper corner and activated the entire mapped tissue within 26 milliseconds. There was a pause of 191 milliseconds between cycles 8 and 9. The pause was defined by the difference between the earliest activation of cycle 8 (858 milliseconds) and the earliest activation of cycle 9 (1049 milliseconds). The ninth activation was entirely different from the previous eight activations and has only one large and coherent wave front in the entire mapped tissue.

Fig 3 shows the actual recordings associated with the isochronal map shown in Fig 2. Double activations were initially seen in electrode E3. After three cycles, the double activations were seen best in electrode B5. This finding implies that the core of the reentrant wave fronts had drifted. The same phenomenon has been observed in in vitro models of reentry.\(^6,8\) Compatible with this hypothesis, the linear core in the first two cycles of reentry (Fig 2A and 2B) was near electrode
E3, whereas in subsequent cycles (Fig 2C and 2D) the location of the linear core changed from the E3 site to areas close to electrode B5.

Fig 3A shows that the reentrant wave front consistently conducted from electrode B4 to B5 until the eighth beat, when abrupt termination was observed. Before the block occurred, a large local activation was registered at 860 milliseconds on channel B5. Fig 3B shows the activations registered in B4, B5, and C5 during the same period in greater detail. The electrode B5 registered double activations. One activation was slightly later than the last activation on channel B4; the other was slightly later than the last activation on channel C5. This pattern is compatible with the electrode recording being near, but not exactly at, the core of the reentry. The electrode at the core of reentrant wave fronts should register double activations that are of equal size. Each deflection of the double activation represents a centripetal wavelet that was unable to propagate beyond the center (core) of reentry. The number in parenthesis shows the deflections that were not included in the isochronal map of Fig 2. Initially, the double activations in B5 showed larger deflections after the activation at B4 and smaller deflections after the activation at C5, indicating that the center of the reentrant circuit was nearer the B4 electrode than the C5 electrode. The relative size of the electrogram reversed in the last activation. The activation that occurred at 860 milliseconds was larger than the one that occurred at 810 milliseconds, indicating that the wavelet had partially penetrated the circuit near electrode B5. On the isochronal map, the time 860 milliseconds is shown in Fig 2D at electrode site B5. Because of this partial penetration, when the leading edge of the reentrant wave front arrived at 910 milliseconds, the tissue had only 50 milliseconds to recover. The wave front could not be conducted to the B5 area, resulting in the termination of the reentrant activity. The arrow in Fig 3B points to a low-amplitude deflection on channel B5, indicating minimal or no propagation of the wave front from B4 to B5. The reentry was abruptly terminated in this area (Fig 2E). On the other hand, because, as was observed in previous cycles, the reentry was able to continue, the duration of 107 milliseconds (the difference between 590 and 697 milliseconds) and the duration of 94 milliseconds (the difference between 710 and 804 milliseconds) must be long enough for conduction to occur.

To determine the ventricular refractory periods during VF, we analyzed the preceding intervals associated with conduction and the preceding intervals associated with block. When block occurred, the leading edge of
the reentrant wave front encountered tissue that had been excited within the past 58±12 milliseconds (range, 28 to 77 milliseconds), which corresponded to 47±12% of the preceding reentrant wave-front cycle length (126±18 milliseconds; range, 89 to 175 milliseconds). This period was significantly shorter (P<.001) than the recovery period in the same region that had allowed conduction (91±19 milliseconds; range, 48 to 137 milliseconds), which corresponded to 72±18% of the preceding reentrant wave-front cycle length (128±17 milliseconds; range, 93 to 177 milliseconds). Note that the preceding reentrant wave-front cycle lengths associated with block did not differ significantly from the preceding reentrant wave-front cycle lengths associated with conduction.

In Fig 4 we plotted the recovery period associated with block (filled circles) and conduction (unfilled circles) against the preceding reentrant wave-front cycle length in all episodes. The figure showed an overlap between the recovery period that allowed conduction and the recovery period associated with block. Because the longest recovery period associated with block was 77 milliseconds and because the shortest recovery period that allowed conduction was 48 milliseconds, the refractory period was estimated to be between 48 and 77 milliseconds.

**Termination by Competition and Interference**

In 29 episodes, the reentrant wave fronts terminated because they encountered interference from other wave fronts. In 9 episodes, these wave fronts came from outside of the mapped region. Fig 5 shows an example. Panels A and B show a counterclockwise reentrant wave front with the earliest excitation close to the center of

![Fig 3](image)

**Fig 3.** Actual recordings of the reentrant wave front shown in Fig 2. A shows that the sequence of activation of the reentrant wave front was in a counterclockwise direction. In the initial four cycles, double activations were registered at electrode E3. Double activations were then registered in electrode B5, indicating a shift of the core of the reentrant wave front. The conduction blocked between B4 and B5 on the eighth cycle. The last activation (cycle 9) on this panel showed a more synchronized activation than the others because the area was activated by one large wave front originating from outside the mapped region. B shows the activations of cycles 5 to 8 in greater detail. See text for details.

![Fig 4](image)

**Fig 4.** Graph showing the recovery period of conducted and blocked wave fronts (ordinate) versus the cycle length in ventricular fibrillation (VF, abscissa). Unfilled circles indicate the recovery intervals that preceded conduction; filled circles indicate the recovery intervals that preceded block. The preceding reentrant wave-front cycle length of both conducted and blocked reentrant wave fronts scattered over the same range. However, the recovery period associated with conduction block was always <77 milliseconds. There is an overlap between the recovery intervals of blocked and conducted wave fronts.
the mapped region. In panel C, activation wave fronts invaded the mapped region from the upper and the lower edges (arrows). These outside wave fronts gradually excited larger areas of the mapped tissue and progressively interfered with the reentrant pathway, terminating the original reentrant wave front (panel D to panel F).

Fig 6 shows actual activations registered in the same episode as shown in Fig 5. The wave front of cycle 5 (C5-D5-C6) was from the original reentrant wave front. The wave front of cycle 6 (D8-C8-D7-C6-D6-C6) was from outside the mapped region. Both wave fronts activated tissue near C6, resulting in a double activation (arrow), and prevented the continuous conduction of cycle 6 (C5-D5) into C6, as had occurred in the preceding cycles. Cycle 7 showed that the original reentrant wave fronts were completely replaced by an activation wave front from outside of the mapped region.

**Unstable Reentrant Wave Fronts and New Wave Fronts**

In 20 episodes, the reentrant wave fronts became unstable and eventually terminated. A new wave front then arose from an area within the mapped region. Fig 7 shows an example. Panels A and B show a counterclockwise reentrant wave front around a linear core. In panel C, the core appeared to drift toward the center of the map. Panel D shows a fractionation of the line of slow conduction or block. Panel E shows an activation block that resulted in the absence of excitation on the left half of the mapped tissue. A new wave front (panel F) arose from the area near electrodes D6 and E6, which became the new origin of the activation.

The difference between Figs 5 and 7 is that in Fig 5 the invading wave front gradually occupied a larger and larger area until it eventually took over the entire area. In Fig 7, however, the extraneous wave front had its effects on the right edge of the mapped tissue. The eventual termination occurred in the lower part and on the left side of the mapped region, remote from the invading wave front from the right edge. Therefore, we have classified them into different patterns.

Fig 8 shows the actual activation registered in the same episode as shown in Fig 7. There was a sudden change in the sequence of activation between activations 3 and 4; the A5-B5-C5-D5 sequence was changed to D5-C5-B5-A5, indicating that the wave fronts were originating from a different site. The mechanisms by which low-amplitude deflections (arrows) occurred near electrode D6 are unknown.
Effect of Myocardial Fiber Orientation on Reentrant Wave Fronts

To determine if the occurrence of conduction block is influenced by local myocardial fiber orientation, we plotted, in Fig 9, all 31 electrode sites associated with conduction block. There is a clustering of the sites in the right lower portion of the mapped region. Because the counterclockwise reentrant wave fronts were propagating across the fibers in this region, Fig 9 indicates that the fronts were traveling perpendicular to the long axis of myocardial fibers when most of the conduction block occurred. Thus, myocardial fiber orientation significantly influences the termination of reentrant wave fronts.

Effect of Subendocardial Ablation on Reentrant Wave Fronts

Effective chemical ablation of the right ventricular subendocardium was confirmed by histopathologic studies. In each mapped tissue specimen, eight sections were examined. In dogs that underwent subendocardial ablation, the Purkinje fibers and the subendocardial contractile myofibers showed changes consistent with early necrosis. The findings were the same as those reported in an earlier study. The layer of necrotic subendocardial myocardial cells approximated a zone of up to six or seven myocardial cells, or roughly a depth of 0.5 mm. In the other three dogs, nuclei were present in 10% to 20% of the Purkinje fibers observed. However, none of these cells had a completely normal appearance.

The reentrant wave fronts and VF were easily induced by premature shocks both before (60 episodes) and after (57 episodes) ablation. Despite chemical ablation of the right ventricular subendocardium, the characteristics of reentrant wave fronts before and after ablation were similar. The reentrant wave-front life span was over 10 cycles in 8 VF episodes before ablation and in 10 VF episodes after ablation (P=NS). In other episodes, the reentrant wave fronts terminated within an average of 3.2±1.9 cycles before ablation and 3.1±1.8 cycles after ablation (P=NS). Abrupt block of reentrant wave fronts was observed in 13 episodes before ablation and in 10 episodes after ablation (P=NS). The reentrant wave fronts induced with either anodal or cathodal shocks had cycle lengths of 118±19 milliseconds at baseline and 124±20 milliseconds after ablation (P<.001). In 41 VF episodes, a single large wave front (Fig 2F) was observed immediately after reentrant wave-front termination. The preceding cycle length of the large wave front was 146±23 milliseconds (n=20) at baseline and 165±42 milliseconds (n=21) after ablation (P=NS). The total activation time of the large wave front averaged 31±12 milliseconds at baseline and 42±12 milliseconds after ablation (P=.005). Therefore, subendocardial ablation significantly prolonged the reentrant wave-front cycle length and the total activation time of the large wave fronts.

Factors That Determine the Total Activation Time

Multivariate linear regression analysis was performed by using total activation time of 41 single large wave fronts as the dependent variable and by using the following two factors as independent variables: (1) preceding VF cycle length (pause since the last activation) and (2) whether or not subendocardial ablation was performed. The results showed that both the immediate preceding VF cycle length (P=.002) and the subendocardial ablation (P<.001) significantly affected the total activation time. Subendocardial ablation prolonged the total activation time, whereas a longer preceding VF cycle length (pause) was associated with a shorter total activation time (Fig 10).

In Table 1, we listed the total activation time during sinus rhythm and the shortest total activation time of the large wave fronts during VF in each dog. Ablation of the subendocardial Purkinje fiber network significantly increased the total activation times during sinus rhythm (P<.001). In each dog, the shortest total activation
times of the large wave fronts during VF also increased after subendocardial ablation. However, the difference of the means did not reach statistical significance ($P = .091$). Table 1 also shows that, after ablation, the shortest total activation time of the large wave front during VF was shorter than the total activation time during sinus rhythm in five of the six dogs studied. This finding could not be explained by the recovery period (411 ± 53 milliseconds for sinus rhythm and longer than 167 ± 56 milliseconds for VF; $P = .001$).

**Effect of Shock Polarity on Reentrant Wavefronts**

Clockwise reentrant wave fronts were easily induced with either cathodal or anodal premature shocks. There was no significant difference in reentrant wave-front cycle length induced with cathodal and anodal shocks both at baseline or after subendocardial ablation with Lugol's solution (Table 2).

**Discussion**

**An Excitable Gap Is Present in the Reentrant Wavefronts**

Ventricular refractory period can easily be measured in sinus or paced rhythm by premature stimulation. However, because the ventricles do not contract synchronously during VF, it is difficult to study the refractory period during this arrhythmia. Many investigators believe that there is no diastolic interval between the
repolarization phase of one action potential and the depolarization phase of the next one and that the cells are reexcited as soon as they recover their excitability.\textsuperscript{22-24} In contrast, other authors\textsuperscript{25,26} reported that, although isoelectric periods were difficult to detect by ECG during VF, intracellular recording demonstrated isoelectric periods at the level of the resting potential. Therefore, the refractory period during VF may not be equal to the VF cycle length.

In the present study, the reentrant wave-front cycle length was 118±19 milliseconds before and 124±20 milliseconds after subendocardial ablation. A recovery period of 91±19 milliseconds (range, 48 to 137 milliseconds) was observed between successive electrode sites during which the next incoming wave front was allowed to conduct and to maintain reentrant excitation. However, if the next incoming wave front arrived 58±12 milliseconds (range, 28 to 77 milliseconds) after the preceding activation, the reentrant wave front could be blocked. A new wave front from outside of the mapped area then activated the tissue studied (Fig 2F). These data indicate that the refractory period during VF varies from 48 to 77 milliseconds. The excitable gap of the reentrant activity, defined as the difference between the activation cycle length and the refractory period, is therefore \( \approx 50\% \) of the activation cycle length. These results are compatible with the data reported in a previous study\textsuperscript{1} that investigated the recovery time needed for reentry to occur after a single strong premature stimulus. In Table 1 of that study, the authors reported that a recovery time of 26±20 milliseconds was

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Dog} & \textbf{Baseline} & \textbf{Ablation} & \textbf{Baseline} & \textbf{Ablation} \\
\hline
1 & 10 & 37 & 22 & 27 \\
2 & 15 & 36 & 15 & 34 \\
3 & 18 & 32 & 29 & 31 \\
4 & 21 & 36 & 11 & 21 \\
5 & 14 & 30 & 14 & 57 \\
6 & 26 & 44 & 28 & 30 \\
\hline
\end{tabular}
\caption{Total Activation Time of Sinus Rhythm and the Shortest Total Activation Time of Large Wave Fronts During Ventricular Fibrillation}
\end{table}

\( ^{*}P<.001 \) compared with sinus rhythm at baseline.

A. BASELINE

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{A.png}
\caption{The correlation between the total activation time of the large wave front during ventricular fibrillation and the preceding recovery interval (pause). A shows the total activation time at baseline. B shows the total activation time after ablation of the right ventricular subendocardium with Lugol’s solution. There is a weak but significant correlation between the total activation time and the preceding recovery interval, or the pause, during ventricular fibrillation.}
\end{figure}
TABLE 2. The Reentrant Wave-Front Cycle Length

<table>
<thead>
<tr>
<th>Shock Polarity</th>
<th>Cathode Wave-Front Cycle Length, ms</th>
<th>Anode Wave-Front Cycle Length, ms</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>116±18 (n=149)</td>
<td>120±20 (n=117)</td>
<td>NS</td>
</tr>
<tr>
<td>Lugol’s Ablation</td>
<td>122±20 (n=131)</td>
<td>126±21 (n=125)</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
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</table>

too short to allow reentrant excitation. Repetitive responses and VF were induced when the recovery time was increased to 68±20 milliseconds and 91±21 milliseconds, respectively. It is also interesting that the duration of the refractory period reported in the present study was similar to the preshock intervals that were associated with the postshock regeneration of VF after an unsuccessful defibrillation shock. These findings imply that, for a shock to reinitiate VF after an unsuccessful defibrillation, it must occur at, or near the end of, the refractory period of the fibrillating ventricular myocytes.

The presence of an excitable gap during VF has been reported. Zhou et al. studied the refractory period during VF by measuring transmembrane action potentials with floating microelectrode techniques. An electric shock was delivered during VF, and the refractory period was estimated by action potential responses. They concluded that the refractory period during VF was 61±5 milliseconds for 5-millisecond monophasic shocks, whereas the mean VF activation cycle length was 86±15 milliseconds. Therefore, =80% of the VF cycle length is inexitable at any instant during VF. In a thin slice of left ventricular epicardial muscle, Davidenko et al. measured the excitable gap of reentrant excitation to be 85 to 127 milliseconds, which represented at least half of the reentrant wave-front excitation cycle length in their in vitro preparation. Pertsov et al. reported that, in their isolated ventricular tissue, the period of spiral wave rotation was 183±68 milliseconds, whereas the refractory period was 131±38 milliseconds. Therefore, a 50-millisecond excitable gap is present. Our results are somewhat different from those reported by these investigators both in terms of the absolute values of the refractory periods and the proportion of the VF cycle length that is refractory. However, differences in the techniques used to measure refractoriness make comparisons between these studies difficult.

Mechanisms of Reentrant Wave-Front Termination

In the present study, we observed several different patterns of activation associated with reentrant wavefront termination. The first pattern was that the functional conduction block near the core of the reentrant wave front was penetrated by one limb of the rotating wave front (Figs 2 and 3). The second pattern was that an outside wave front penetrated the core of the reentrant wave front and blocked its propagation (Figs 5 and 6), similar to the phenomenon observed in the in vitro preparation, when a wave front initiated by a premature stimulus could terminate reentry. The third pattern was that the core of the reentrant wave fronts drifted, and the area of slow conduction or block changed in each successive beat, until the rotation wave front was terminated. It is reasonable to assume that the presence of an excitable gap during VF is important for these patterns of activation to occur.

Some activation patterns in VF cannot be explained simply by the presence of an excitable gap. For example, a focal type of excitation pattern was sometimes observed after the reentrant wave fronts terminated. A similar focal pattern of activation has been reported previously for VF and for ventricular tachycardia. One explanation for the occurrence of this pattern was that a microreentrant circuit was present at the origin of the excitation. Because the reentrant circuit was smaller than 3 mm, reentrant patterns were not clearly demonstrated. Low-amplitude activations near the early site (arrows in Fig 8) suggest that microreentry may be present in that area. A second explanation is that the wave fronts actually originated from outside of the mapped tissue but were conducted to the mapped area via transmural propagation. The epicardial breakthrough of these wave fronts appeared focal. Other mechanisms, such as automaticity and triggered activity, could not be entirely ruled out.

Myocardial Fiber Orientation and Reentrant Wave-Front Termination

The reentrant wave fronts observed in the present study appeared to have a linear core around which activity circulated. This finding indicates that tissue anisotropy plays an important role in determining the patterns of activation during reentry. In the present study we also found that, in most episodes, conduction block occurred when the wave fronts were traveling across the myofibers. Although it has been reported that the safety factor of impulse propagation is higher across than along the fiber under normal conditions, recent computer simulation and isolated tissue experiments have suggested that, when active membrane properties are impaired, the safety factor for propagation is larger in the direction along the longitudinal axis of fibers. Because the myocardial cells during ventricular fibrillation have a shorter action potential duration and a smaller amplitude than during normal rhythm, the safety factor of propagation during VF may be more compatible with that of the impaired cells. If so, our results are compatible with the results of computer simulation and in vitro studies.

Effect of Subendocardial Ablation on Reentrant Wave Fronts

It is believed that preexisting structural and functional inhomogeneities in the myocardium are responsible for the generation and the maintenance of reentrant arrhythmias. Because Purkinje fibers have structural and functional characteristics that are different from the ordinary myocardial cells, they may contribute to the inhomogeneities of the myocardium and therefore play an important role in arrhythmogenesis. Compatible with this hypothesis, several groups of investigators found that the subendocardium is more important than are the other parts of the ventricle in the generation and the maintenance of VF. However, because the actual reentrant wave fronts during VF were not mapped in these studies, the mechanisms by which Purkinje fibers and the subendocardial myocytes...
Contribute to the generation and the maintenance ofVF are unknown.

In a previous study,12 we demonstrated that, in the in situ ventricles, subendocardial ablation does not prevent the electrical induction ofVF. In the present study, we further demonstrated that reentrant wave fronts could be easily induced both before and after effective subendocardial ablation. Although subendocardial ablation slightly prolonged reentrant wave-front cycle length, it did not affect the reentrant wave-front life span. These findings indicate that the initiation and the maintenance of reentrant wave fronts and VF cannot be prevented by chemical subendocardial ablation.

Limitation of the Subendocardial Ablation Techniques

The results of the present study, however, cannot be used to support the conclusion that Purkinje fibers are not important in VF. Schap et al13 reported that they were able to record Purkinje potentials up to 3 mm beneath the endocardial surface in the left ventricular free wall and up to 1 or 2 mm in the right ventricular free wall. The subendocardial cell necrosis produced by topical application of Lugol’s solution measured only 0.5 mm in depth.21 Although we did not find any normal-looking Purkinje fibers in the histological sections, microscopic differentiation between Purkinje fibers and myocardial cells may be difficult. Therefore, some Purkinje fibers may have survived and thus contributed to the generation and maintenance ofVF. Another limitation of the present study is that the mapping and histopathologic studies were limited to only a small part of the right ventricle. Further studies will be needed to prove that these findings can be generalized to other parts of the ventricles.

Propagation of Wave Fronts During VF

We demonstrated in the present study that, at least for single large wave fronts, the epicardial total activation time during VF was influenced by the presence or absence of the Purkinje fiber network and the recovery period since the previous excitation. These findings, however, could not explain the fact that, in five of the six dogs after ablation, the shortest total activation time of the large wave front was shorter than the total activation time during sinus rhythm (Table 1). An explanation for this very short total activation time during VF is that there is a difference between the amount of transmural activation during VF and during sinus rhythm. Because we did not perform transmural recordings, this hypothesis cannot be proven by the present study. A second possible mechanism is that a period of supernormal conduction was present. However, Fig 10 does not show a period of supernormal conduction to support this hypothesis.

Cobb et al14 reported that an electric countershock can excite the intracardiac cholinergic and adrenergic nerves. It is possible that the 50-V shock used to induce the reentrant wave fronts may have excited the intracardiac autonomic nerves, which in turn increased the velocity of the wave-front propagation. We do not have data to support this hypothesis.

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References

38. Friedman PL, Stewart JR, Wit AL. Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res. 1973;33:612-626.
39. Friedman PL, Fenoglio JJ Jr, Wit AL. Time course for reversal of electrophysiological and ultrastructural abnormalities in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res. 1975;36:127-144.
The mechanism of termination of reentrant activity in ventricular fibrillation.
Y M Cha, U Birgersdotter-Green, P L Wolf, B B Peters and P S Chen

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