High-Current Stimuli to the Spared Epicardium of a Large Infarct Induce Ventricular Tachycardia

Katherine M. Kavanagh, MD; J. Scott Kabas, MD; Dennis L. Rollins, MS; Sharon B. Melnick, AAS; William M. Smith, PhD; and Raymond E. Ideker, MD, PhD, FACC

Background. Previous studies have demonstrated that both ventricular tachycardia (VT) and ventricular fibrillation (VF) may begin as figure-eight reentry: VT with a longer cycle length from spared tissue adjacent to an infarct by programmed stimulation and VF with a shorter cycle length from noninfarcted tissue by a large premature S₂ stimulus. These results suggest that the type of tissue or cycle length of the arrhythmia rather than the mode of induction determines whether the figure eight becomes sustained VT or degenerates into VF. Thus, a protocol similar to that by which a VF threshold is determined may induce VT rather than VF when performed in the spared tissue over an infarct.

Methods and Results. In 10 dogs, 4 days after occlusion-reperfusion of the left anterior descending coronary artery, 10 S₁ stimuli were delivered from a total of 34 right and left ventricular sites outside the infarct. An epicardial S₁ stimulus over the infarct was increased in 10-mA steps and introduced in diastole at decreasing cycle lengths of 5 msec until VT or VF was induced. Sustained monomorphic figure-eight VT was induced from 24 S₁ sites and VF from nine (p=0.03). The mean cycle lengths for the initial six arrhythmic cycles was 152±33 msec for VT and 115±13 msec for VF (p<0.001). Mean transmural infarct extent was 80% in five dogs with only VT, 63% in three dogs with both VT and VF, and 15% in two dogs with only VF. Different morphologies of VT were induced by changing the S₁ site, the S₂ strength, or the S₁S₂ coupling interval. In 25 of the 34 arrhythmias, the central part of the initial figure-eight pathway was oriented opposite the S₁ activation sequence in that region.

Conclusions. A large S₁ stimulus over a nontransmural infarct induces VT if the spared myocardium is thin. This study introduces a useful technique for inducing sustained monomorphic VT in which the location and direction of the figure-eight pathway are known a priori and in which different morphologies of sustained VT can be produced by changing the S₁ site.

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Figure-eight reentry is one of several mechanisms by which ventricular arrhythmias can occur. Experimental studies, using different canine models and different modes of electrical induction, have demonstrated a figure-eight reentry pattern during both ventricular tachycardia and the initial cycles of ventricular fibrillation.¹⁻³ Wit et al¹ and El-Sherif et al² have demonstrated figure-eight reentry in the surviving epicardium over a 4-day-old infarct in a canine model using programmed stimulation in which a small S₂ (<2 mA) was given outside the infarct. By using a high-current premature S₂ (>20 mA) during the vulnerable period in a noninfarcted canine model with S₁ pacing a few centimeters away from the S₂ site, Chen et al³ have demonstrated figure-eight reentry during the initiation of ventricular fibrillation. The cycle length of successive activations during the figure-eight reentry observed in the Chen³ study was shorter than that observed in the studies of sustained ventricular tachycardia.

The same mode of induction does not always result in the same type of arrhythmia. For example, both
ventricular tachycardia and ventricular fibrillation have been induced by programmed stimulation in the presence of a myocardial infarction.\textsuperscript{4,5} Wolff \textit{et al}\textsuperscript{6} have demonstrated that transthoracic shocks during the vulnerable period in infarcted animals frequently induced ventricular tachycardia in which only ventricular fibrillation could be induced before infarction. However, the effect of applying a high-current premature stimulus directly to the spared epicardium of an infarct has not been systematically investigated.

Janse \textit{et al}\textsuperscript{7} have shown that ventricular fibrillation was frequently initiated in isolated, Langendorff-perfused, canine hearts in which ischemia was induced. However, after destroying the subendocardium with phenol and leaving the epicardium electrophysiologically normal, ventricular tachycardia and not fibrillation was initiated. A similar finding has been reported by Allessie \textit{et al}\textsuperscript{8} for isolated rabbit hearts in which most of the ventricular myocardium was made necrotic by freezing except for a thin rim of epicardial sparing.

The results of the previously discussed in vivo and in vitro studies suggest that neither the mode of induction nor the initial activation pattern (figure-eight) are primarily responsible for determining whether ventricular tachycardia or ventricular fibrillation is induced: Rather, their induction may be correlated with the thickness of the myocardium in which this activation pattern is induced and the cycle length of the activation pattern. Thus, a high-current premature stimulus during the vulnerable period over the surviving epicardium of a 4-day-old infarct in a canine model may induce sustained ventricular tachycardia with a figure-eight reentry pattern rather than ventricular fibrillation. The purpose of the present study was to test this hypothesis.

\section*{Methods}

\textbf{Surgical Preparation}

\textit{Part 1: Left anterior descending coronary artery occlusion.} In 12 mongrel dogs, anesthesia was induced using intravenous thiopental sodium (20 mg/kg) and was maintained using a continuous infusion of thiopental sodium at a maintenance rate of approximately 0.8 mg/kg/min. Succinyicholine (1 mg/kg) was also given at the time of anesthesia induction. The animals were intubated with auffed endotracheal tube and ventilated with room air and oxygen through a Harvard respirator (Harvard Apparatus Co., South Natick, Mass.). A femoral arterial line and two intravenous lines were inserted using sterile techniques. Systemic arterial pressure was continuously displayed. Arterial blood samples were drawn every 30–60 minutes for determination of pH, $P_{O_2}$, $P_{CO_2}$, base excess, bicarbonate, Na$^+$, K$^+$, and Ca$^{2+}$ content. Ringer's lactate was continuously infused via a peripheral intravenous line. This was supplemented with sodium bicarbonate, potassium chloride, and calcium chloride as indicated to maintain pH and electrolytes within normal values. Electrocardiographic leads were applied for continuous ECG monitoring. Body temperature was maintained with a thermal mattress. With sterile surgical techniques, the heart was exposed through a left thoracotomy at the fourth intercostal space; the pericardium was opened, and the left anterior descending coronary (LAD) artery was dissected free at the tip of the left atrial appendage. A noose occluder was placed around the LAD, and it was occluded by the Harris two-stage procedure.\textsuperscript{9} To ensure sparing of the epicardium in the entire infarct zone, partial occlusion was maintained for 30 minutes, followed by complete occlusion for 90 minutes before reperfusion. Five minutes before initiation of partial occlusion and again before the termination of complete occlusion, the animals were pretreated with bolus injections of intravenous lidocaine (2 mg/kg). A second bolus of lidocaine (1 mg/kg) was administered 10 minutes later. The chest was closed in layers, evacuated under negative pressure, and the animal was allowed to recover.

\textit{Part 2: Placement of electrodes.} Four days after LAD occlusion, anesthesia was induced with intravenous pentobarbital (30–35 mg/kg body weight) and maintained with a continuous infusion of pentobarbital at a rate of approximately 0.05 mg/kg per minute. Succinyicholine (1 mg/kg) was also given intravenously at the time of anesthesia induction. Supplemental doses of 0.25–0.5 mg/kg succinyicholine were given hourly as needed to maintain muscle relaxation. The animals were ventilated, hemodynamically monitored, and maintained as described above. A median sternotomy was performed, and the heart was suspended in a pericardial cradle. The recording apparatus consisted of 121 bipolar Ag-AgCl epicardial electrodes\textsuperscript{10} arranged in 11 columns and 11 rows mounted in a 4×4-cm plaque. Each epicardial electrode was 1 mm in diameter. There was a 2-mm intraelectrode distance between each member of the bipolar pair and an interelectrode distance of 4 mm. This plaque also contained a centrally located stimulating electrode. The plaque of epicardial recording electrodes was sutured over the infarcted anterior surface of the left ventricle (Figure 1). Four solid stainless steel wires (American Wire, gauge No. 30, Cooner Wire Co., Chatsworth, Calif.) that were insulated except at the tip were positioned for $S_1$ pacing from the lateral right ventricle, the right ventricular outflow tract, the lateral left ventricle, and the posterior left ventricle. Defibrillating patches were sutured over the right atrium and upper portion of the lateral right ventricle and the posterior apical left ventricle to deliver cardioversion or defibrillation shocks. Limb leads I, II, and III were recorded with limb lead II bandpass filtered from 50 Hz to 300 Hz so it recovered quickly after large premature stimuli.

\section*{Data Acquisition}

A computer-assisted mapping system capable of simultaneously recording 128 channels was used to record the stimulus potentials in unipolar mode with
the left leg as reference and the activation complexes in bipolar mode. Signals were recorded digitally at a rate of 1,000 samples per second with a low-pass filter at 500 Hz and the high-pass filter at 5 Hz. Gain settings for each channel were individually adjusted for optimum recording. The data were stored on videotape for off-line analysis. The recordings from each channel were subsequently displayed on a SUN 3/60 workstation to allow measurement of stimulus potentials and detection of activation times.

Definitions

The ventricular refractory period for a particular strength \( S_2 \) was defined as the largest \( S_2 \) interval that failed to evoke a ventricular response. In this study, inducible sustained monomorphic ventricular tachycardia was defined as an ECG sequence of uniform ventricular depolarizations at a cycle length of less than 400 msec that lasted more than 30 seconds or produced hemodynamic compromise requiring immediate cardioversion.

Stimulation Protocol

Unipolar cathodal pacing at a pulse width of 5 msec was used to determine late diastolic threshold at each of the five stimulation sites (two right ventricular sites, two left ventricular sites, and the center of the recording plaque). The propensity for sustained ventricular tachycardia was assessed by pacing at a cycle length of 300 msec for 10 beats \((S_2)\) at twice diastolic threshold followed by an extra stimulus \((S_2)\) consisting of a 5-msec square wave that was given to scan diastole at 5-msec intervals or less. The \( S_1 \) train was delivered from one of the four pacing sites outside of the plaque of recording electrodes, whereas \( S_2 \) was always delivered from the center of the plaque. Diastole was scanned by decreasing the \( S_1S_2 \) coupling interval in steps of 5 msec. The initial strength of the \( S_2 \) was 10 mA. If diastole was scanned without the induction of ventricular tachycardia or ventricular fibrillation and the ventricular refractory period was reached, the strength of the \( S_2 \) was increased by 10 mA and scanning was repeated. Once ventricular tachycardia or fibrillation was initiated and halted by cardioversion or defibrillation, the procedure was repeated using a new \( S_1 \) site with the initial \( S_2 \) strength set equal to that which induced the arrhythmia at the previous \( S_1 \) site. This protocol was repeated at all four \( S_1 \) sites. After ventricular dysrythmias were initiated from all four \( S_1 \) sites, the strength of the \( S_2 \) was increased in 10-mA steps to a maximum of 100 mA for one of the \( S_1 \) pacing sites.

Histological Examination

At the end of each experiment, the heart was excised, weighed, and fixed in formalin. A histological section was taken perpendicular to the epicardium through the center of the infarct zone beneath
the recording plaque to determine the thickness of the infarcted and of the subepicardially spared myocardium. On either side of this perpendicular section, serial sections were taken every 0.5 mm parallel to the epicardium in the infarct zone to determine fiber orientation of the spared epicardial tissue. All sections were stained with hematoxylin and eosin.

Data Analysis

The recordings from each channel were displayed on a Sun 3/60 computer workstation. In all dogs, the last two activations of the S1 train and all activations after the S2 stimulus until the ventricular tachycardia settled into uniform repeatable complexes on the surface ECG were analyzed. When ventricular fibrillation instead of ventricular tachycardia was induced, the initial six activation complexes after the S2 stimulus were chosen for analysis. The time selected for each activation was the fastest slope for biphasic complexes and the absolute peak value for monophasic and multiphasic complexes.14 Electrodes with saturated signals or with signals too noisy to identify activations reliably were not analyzed. Isochronal maps were drawn for all complexes analyzed. A heavy black bar was used to indicate block between neighboring electrodes when 1) activation times differed by more than 40 msec (conduction velocity <0.1 m/sec).15-17 and 2) double activations were seen in the electrodes bordering the line of block in which one complex corresponded in time to the activation front on one side of the block and the other complex corresponded to the activation front on the other side of the line of block. Hatched bars were used to represent the frame lines between sequential isochronal maps. The term "frame line" is used to indicate that the activation front does not stop at the line, but that the frame lines represent the break points between maps that are necessary to represent the dynamic continuous activation sequence of reentry by a series of static discrete isochronal maps.

With voltage dividers,11 potentials were measured at the 121 recording electrodes for 10-msec monophasic shocks equal in strength to the lowest current inducing the tachyarrhythmia at all four S1 sites. Potentials were also recorded for stronger shocks in increments of 20 mA to a maximum of 100 mA. Unipolar potentials were measured at each recording site, relative to the preceding baseline, at a consistent point 3-4 msec into the shock. A 10-msec stimulus was used to measure the S2 potentials instead of the 5-msec stimulus used for S2 induction of the arrhythmia because a short spike lasting 1-2 msec was present in the recordings at the onset and the offset of the S2 stimulus. The potential gradient was calculated from the potentials and the interelectrode distances by a finite-element method.18

Statistical Procedures

Student's t test19 was used to analyze differences in means. $\chi^2$ analysis20 was used to analyze differences in populations. Data are presented as mean±SD. Significance was defined as $p \leq 0.05$.

Results

Twelve mongrel dogs weighing 23.5±1.6 kg were the subjects of this study. One of the 12 died in the first 12 hours after LAD occlusion. A second dog died 4 days after infarction during anesthesia induction for the placement of electrodes. Therefore, arrhythmia induction was attempted in 10 animals. In two of the 10 dogs, the S2 threshold for ventricular arrhythmia (sustained ventricular tachycardia or ventricular fibrillation) induction had been determined for only one of the S1 pacing sites before the animals died. In the remaining eight animals, the S2 arrhythmia threshold stimulus was determined for all four S1 pacing sites. Thus, the S2 arrhythmia threshold stimulus was determined for a total of 34 sites in the 10 animals (Table 1). Sustained monomorphic ventricular tachycardia was induced from 24 of these sites, ventricular fibrillation from nine sites, and sustained polymorphic ventricular tachycardia was induced from one S1 site. The episode of polymorphic ventricular tachycardia was eliminated from all statistical analysis. By $\chi^2$ analysis, the incidence of monomorphic ventricular tachycardia was significantly different from ventricular fibrillation ($p=0.03$).

Figure 2 shows an example of monomorphic ventricular tachycardia induced in a dog with an 80% transmural infarct. The S1 pacing site was the right ventricular free wall and the S2 stimulus was 20 mA, which is the lowest-strength S2 stimulus that induced tachycardia in this animal. The activation front initiated by S1 stimulation enters from the upper left corner, which is the area closest to the S1 pacing site (Figure 2A). The front then conducts diagonally across the tissue under the plaque, following the long axis of the myocardial fibers. The earliest activations after S2 stimulation are recorded on the left side of the plaque toward the S1 site (Figure 2B), which is

### Table 1. Number of S1 Sites Inducing Ventricular Tachyarrhythmias

<table>
<thead>
<tr>
<th>Dog</th>
<th>With SMVT</th>
<th>With VF</th>
<th>Transmural extent of infarct (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
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<td>0</td>
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</tr>
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<td>3</td>
<td>1</td>
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</tr>
<tr>
<td>7</td>
<td>2†</td>
<td>1</td>
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<td>20</td>
</tr>
<tr>
<td>10*</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

SMVT, sustained monomorphic ventricular tachycardia; VF, ventricular fibrillation.

* Died after first arrhythmic event.
† Died after first arrhythmic event.

Polymorphic ventricular tachycardia from an additional S1 site.
leads face indi4cates interval Isochronal to ventricular tachycardia beats between panels between beats between beats and three, respectively. Panel G: Tracings show monomorphic ventricular tachycardia as recorded by surface leads I, II, and III. Closed arrow indicates S2.

**FIGURE 2.** Mapping of initiation of sustained ventricular tachycardia settling into a monomorphic figure-eight reentry pattern. The activation times and isochronal maps of the last beat of the S1 train (panel A) are shown as well as the first five beats of ventricular tachycardia (panels B–F) induced after a 20-mA _S_2 stimulus at an _S_1_ S_2 interval of 210 msec as recorded by a plaque of 121 bipolar electrodes over the infarct in the left ventricle. (Figures 5–11 are from the same animal as in this figure; _S_1 _S_1 interval of the pacing train is 300 msec for all figures.) The long axis of the spared myocardial fibers is represented by the double-headed arrow at the top of the figure. Each number gives the activation time (msec) at an electrode site. Dots represent sites of inadequate recordings. Isochronal interval is 20 msec. In panel A, time zero is the beginning of the _S_1 train. In panels B–F, time zero is the beginning of the _S_2 stimulus. In panel B, the first beat after _S_2 stimulation, arrows indicate that the activation fronts conduct around both sides of a line of block (represented by the heavy black bar in this and subsequent figures). The hatched line (in this and subsequent figures) represents a frame line between panels in which reentry is assumed to occur. In panel C, the adjoining solid and hatched lines indicate block between beats one and two and reentry between beats two and three, respectively.
Figure 3. Mapping of initiation of sustained monomorphic ventricular tachycardia with figure-eight reentry pattern in an animal in which the S₁ was delivered from the right ventricular free wall. Activation times and isochronal maps of the last beat of the 300-msec S₁ train (panel A) as well as those of the first three beats of ventricular tachycardia (panels B–D) induced by a 30-mA S₂ stimulus at an S₁S₂ interval of 230 msec are shown. In panel B, the activation pattern of the first beat before S₂ stimulation is compatible with figure-eight reentry. Initial activation sequence is directed back toward the S₁ stimulation site in the direction opposite the S₁ activation sequence. Figure-eight reentry is also seen in subsequent beats of ventricular tachycardia (panels C and D). Panel E shows lead II rhythm strip of ventricular tachycardia induced. Open arrow indicates first S₁ and closed arrow indicates S₂. Long axis of the spared myocardial fibers is represented by the double-headed arrow at the top of the figure.

more recovered than the right and bottom sides at the time of S₂ stimulation. The activation fronts then conduct to the right around both sides of a line of block (represented by the heavy black bar). There is a 71-msec time difference between the latest activation time recorded in the initial ventricular tachycardia beat (Figure 2B) and the earliest activation time recorded in the next beat (Figure 2C), and double complexes are recorded at these sites. Therefore, block is assumed present between the late site in Figure 2B and the adjacent early sites in Figure 2C, and it is unclear how or whether the first beat conducted to the second. The fact that earliest activation sites for the second ventricular tachycardia beat are not at the edge of the plaque as for the first beat but are next to the line of assumed block raises the possibility that reentry did occur, although it was undetected in the recordings. Activation then sweeps around the upper line of block and possibly sweeps also around the lower line of block, although this is not definite because the lower line of block extends to the edge of the plaque (Figure 2C). The latest activation time in this beat is 31 msec before the earliest activation time recorded in the third tachycardia beat (Figure 2D), and double complexes are no longer observed in this region. Thus, reentry is assumed to occur between these two beats. The central line in Figure 2C is shown solid to the left and hatched to the right to represent block between beats 1 (Figure 2B) and 2 (Figure 2C) and reentry between beats 2 (Figure 2C) and 3 (Figure 2D). The hatched line is a frame line between successive panels that is necessary to represent reentry by a series of isochronal maps. A similar activation pattern is seen for the next three beats (Figure 2, D–F) with slight changes in the lines of block from beat to beat. By the fifth beat, the lower line of block has shortened, so that a clear figure-eight reentry pattern is present (Figure 2F). The tachycardia was stable after the fifth beat, with only minimal changes in the frame and block lines in subsequent activation sequences. Conduction through the isthmus stabilized after the seventh beat.

In 19 of the 33 episodes of ventricular tachyarrhythmias induced by stimulation from the various S₁ pacing sites, it was possible to identify the initial activation sites of the first beat of the arrhythmia. Earliest post-S₂ activation was never recorded from the region immediately adjacent to the S₂ electrode.
In 14 of these 19 episodes, initial activation occurred somewhere between the S₁ and the S₂ stimulation site and generally conducted in the direction away from the S₁ electrode and toward the S₂ electrode, in the opposite direction to the S₁ activation sequence (Figures 3 and 4). In the other five episodes, the initial post-S₂ activation of the arrhythmia appeared to conduct into the recording area from outside the plaque (Figure 2B). In the remaining arrhythmia episodes, the initial activation sites of the first arrhythmia beat could not be identified because of post-S₂ stimulation saturation of a large percentage of the recording electrodes. However, by the second beat, it could be identified that the activation front was in the opposite direction of the S₁ activation sequence in 25 of the 33 arrhythmia episodes.

Effect of Increasing the S₂ Stimulus

Increasing the strength of the S₂ stimulus to 100 mA continued to induce ventricular tachycardia and not ventricular fibrillation in all animals in which monomorphic ventricular tachycardia occurred. Figures 5–7 show two consecutive cycles after the tachycardia stabilized for 30-, 50-, and 70-mA S₂ stimuli for the same S₁ stimulus and animal shown in Figure 2. The activation patterns suggest figure-eight reentry, although in Figures 6 and 7, part of the figure-eight is outside the recording plaque. In most cases, when ventricular tachycardia has been established, the central portion of the figure-eight pathway is opposite in direction to the activation sequence in that region during S₁ pacing. The locations of the reentrant pathway and the lines of block are very different in Figures 5, 6, and 7. However, the morphological characteristics of the ECG limb leads I, II, and III in each of these Figures (5E, 6E, and 7E) are basically the same as those in Figure 2G. Thus, different S₂ strengths with the same S₁ site led to different activation sequences of monomorphic sustained ventricular tachycardia, but these different morphologies of tachycardia could not be differentiated by the three ECG limb leads recorded. The epicardial potential gradient field generated by the 30-, 50-, and 70-mA S₂ stimuli are shown in Figures 5D, 6D, and 7D, respectively. The highest gradients are located at the center of the plaque in the area of the S₂ and increase with increasing S₂ strength. Because the activation patterns change for several cycles before stabilizing, the center of the figure-eight reentrant circuit is not always precisely in the center of the high-gradient area at the S₂ site but is usually within 1–2 cm of this site. Similarly, the central lines of block for the two reentry rotors are not always precisely at the same level of potential gradient.
Effect of Changing the S2S2 Coupling Interval

In Figure 8, the S1 pacing site and S2 strength remain the same as in Figure 7; however, the S2S2 interval has been decreased from 220 msec in Figure 7 to 170 msec in Figure 8. This change in the S2S2 coupling interval resulted in a figure-eight reentry pattern with a different activation sequence from that seen in Figure 7. Despite a different activation pattern, the surface ECG recordings are relatively unchanged from the previous examples in Figures 2, 5, 6, and 7.

Effect of Changing the S1 Stimulation Site

In four animals, sustained, monomorphic ventricular tachycardia was induced by S2 stimulation following pacing from all four S1 sites (Table 1). The different activation patterns during S1 pacing from different sites caused the activation patterns of the tachycardia to differ (Figures 3 and 4). In Figures 9, 10, and 11, the activation patterns for the sustained tachycardias are shown after pacing from the other three S1 sites for the same animal as for Figures 2 and 5–8. The S2 stimulus given from the center of the plaque is 30 mA in all three cases. Complete (Figures 9 and 11) or incomplete (Figure 10) figure-eight reentry patterns are seen with different locations and orientations. The central portion of the figure-eight pathway conducts in approximately the direction opposite to the activation pathway in the same region during S1 pacing, except in Figure 10, in which the direction of the activation during S1 pacing at the center of the reentrant circuit is unclear. An area of block is seen with S1 pacing from the posterior left ventricle with S1 pacing in Figure 11A. This was not seen in any of the other S1 pacing sites in this animal or from any of the S1 pacing sites in any of the other animals. Even though the tachycardia activation patterns are markedly different, the ECG limb lead recordings are again almost unchanged from those in earlier figures (Figures 2 and 5–10).

Reproducibility of Induced Tachycardias

In four cases, the reproducibility of the tachycardia activation sequence was investigated by repeating the stimulation sequence and the S2 strength that initially induced the arrhythmia. Panels A and B of Figure 12
show the figure-eight activation sequence induced after the induction of ventricular tachycardia by a 30-mA S₂ at an S₁S₂ interval of 230 msec after an S₁S₃ train at 260 msec. A similar activation pattern is seen in panels D and E of Figure 12 after reinduction of ventricular tachycardia with the same stimulation protocol 5 minutes later.

Comparison of Ventricular Tachycardia and Fibrillation Induction

Sustained monomorphic ventricular tachycardia was the only arrhythmia induced in five dogs. In these animals, the mean transmural infarct extent was 80% (Table 1). Ventricular fibrillation was the only arrhythmia induced in two dogs. In these animals, the mean transmural extent of the infarct was 15%. Both ventricular tachycardia and fibrillation were induced in three dogs in which the transmural extent of the infarct was 63%.

Figure 13 shows the activation sequence for one of the episodes of ventricular fibrillation. Figure-eight reentry could still be seen clearly in the 13th and 14th cycles of ventricular fibrillation. The rhythm strip is still relatively organized at beats 13 and 14 despite a rate of 550 beats per minute. The complexes, however, are not completely uniform and the rhythm is irregular, although it is difficult to detect the irregularity in Figure 13D because of the fast rate and slow recording speed. By the 24th cycle, the activation sequence had changed so that no evidence of figure-eight reentry was observed under the plaque.

By the second beat in 25 of the 33 episodes of ventricular tachyarrhythmias, the earliest activations of the induced arrhythmia conducted in the opposite direction to the S₁ activation sequence. This was significant at a value of p ≤ 0.01. No significant difference in this activation sequence was seen for ventricular tachycardia (19 of 24 episodes) and ventricular fibrillation (six of nine episodes). The smallest S₂ stimulus inducing ventricular tachycardia was 38 ± 16 mA versus 57 ± 14 mA for ventricular fibrillation (p ≤ 0.005). The mean arrhythmia cycle length for the initial six cycles after the S₂ stimulus was longer for ventricular tachycardia (152 ± 33 msec) than for ventricular fibrillation (115 ± 13 msec, p ≤ 0.001).

ECG Findings

The three limb leads during episodes of ventricular tachycardia with different figure-eight activation patterns were compared. Only the first episode of tachy-
The ventricular fibrillation threshold is commonly evaluated by giving a large $S_2$ stimulus as a second shock immediately following a first shock and by examining the response on the ECG (panel E Figure 6D). It is always possible to induce ventricular fibrillation with a large stimulus, but the question is whether this can be done predictably and with sufficient regularity to create a reentrant circuit. Thus, the repeatability of the induction of ventricular fibrillation is dependent on the heart's ability to sustain reentry after the large stimulus.

Discussion

The ventricular fibrillation threshold is commonly evaluated by giving a large $S_2$ stimulus immediately following a first shock and by examining the response on the ECG (panel E Figure 6D). It is always possible to induce ventricular fibrillation with a large stimulus, but the question is whether this can be done predictably and with sufficient regularity to create a reentrant circuit. Thus, the repeatability of the induction of ventricular fibrillation is dependent on the heart's ability to sustain reentry after the large stimulus.
figure-eight reentry pattern will have a longer cycle length and result in ventricular tachycardia rather than ventricular fibrillation.

It has previously been reported in canines that 1) the bigger the infarct, the greater the likelihood of ventricular tachycardia induction, and 2) the ventricular fibrillation threshold outside the infarct is decreased in dogs in which ventricular tachycardia is induced by programmed stimulation. However, this study demonstrates that the fibrillation threshold is greatly increased in the spared myocardium over large nearly transmural infarcts; even S2 stimuli as large as 100 mA do not induce fibrillation. Instead, these large premature stimuli induce tachycardia. There are several possible reasons why figure-eight reentry patterns remain stable as sustained ventricular tachycardia in a thin rim of spared epicardium over a 4-day-old reperfused infarct. For example, two-dimensional reentry, as in a thin rim, may be inherently more stable than three-dimensional reentry, as in the total thickness of the noninfarcted ventricular free wall, even if the cycle lengths are the same. However, the finding that the cycle length of the initial figure-eight reentry is slower for ventricular tachycardia suggests that cycle length is also important. This raises the question of why the mean cycle length of the arrhythmia induced by a large S2 in a thin rim of spared epicardium over a large 4-day-old infarct is longer than when the tissue is normal or the infarct is small.

It is possible that some or all of the surviving tissue over the infarct is abnormal 4 days after infarction. The larger and thicker the infarct, the thinner the layer of spared tissue and the more likely the spared tissue at the epicardium is to be abnormal. Four days after infarction, surviving cells have been shown to exhibit decreased $V_{\text{max}}$, elevated resting potentials, cellular uncoupling, and increased refractory periods. All of these abnormalities would be expected to decrease conduction velocity and increase the time to complete one revolution within the reentry circuit, causing an increased cycle length.

Recent evidence suggests that stimulation of a thin layer of myocardium, even if it is normal, leads to ventricular tachycardia but not fibrillation. Using a Langendorff-perfused, noninfarcted rabbit heart...
function at the myocardial fibers. However, with liquid nitrogen, these fibers could be induced with the same stimulation. In their preparation, the electrophysiological properties of the thin rim of surviving tissue remained normal before and after endocardial cryoablation. The present study extends the results of Allessie et al by suggesting that a thin rim of tissue is needed just in the region containing the reentry circuit, not over the entire left ventricle, to cause tachycardia.

Anisotropy of conduction may be responsible for a longer cycle length of reentry in a thin layer of normal tissue. Because of this anisotropy, cardiac impulses propagate approximately three times faster in the direction parallel to the long axis of the myocardial fibers compared with conduction in the transverse direction. Because of the three-dimensional geometry of the normal intact heart with fibers at different transmural levels oriented in different directions, the anisotropy of conduction may be lessened by the fast impulse spreading along fibers at various transverse levels. In the thin rim of normal, spared tissue, Allessie et al found that slow conduction perpendicular to the long axis of the epicardial fiber orientation (i.e., in the transverse direction) proceeded over a longer distance than in the intact heart, where fibers in deeper layers running in other directions provide alternative routes for rapid conduction along fibers. Thus, the absence of deeper layers may unmask the anisotropic properties of the ventricular myocardium, resulting in the induction of a figure-eight reentry pattern with a slower cycle length.

**New Technique for Ventricular Tachycardia Induction**

In animal models of infarction, ventricular tachycardia is most often induced by programmed stimulation and frequently requires up to three extra stimuli. The frequency of induction of this arrhythmia is variable and has been reported to be as low as 20%. The yield can be increased by increasing the number of stimulation sites. In one study in which the yield for ventricular tachycardia induction...
was 100%, the mean number of induction sites assessed per animal was 10±5 SD. Sites with normal excitability and refractoriness within 2 cm of the infarct have the greatest yield at 61%. In the present study, the technique of giving a large S1 stimulus to only one site (the epicardium of the infarct area) resulted in the induction of ventricular tachycardia in eight of 10 animals.

This technique has several advantages besides induction of tachycardia in the majority of animals. It usually gives rise to multiple different, sustained ventricular tachycardias depending on the S1 activation sequence and the S2 strength and timing. This technique also has the advantage that some characteristics of the induced arrhythmia can be predicted a priori. The initial activation front of the induced arrhythmia is in the opposite direction to the spread of the S1 activation front in 76% of induced ventricular tachycardias. The center of the figure-eight is usually within a few centimeters of the site of the S2 stimulation. Knowing the site of initiation of ventricular tachycardia allows the concentration of multiple cardiac mapping electrodes in the area of the initiation stimulus in advance of arrhythmia induction. Thus, this technique provides several variables that may be manipulated to facilitate the investigation of interventional therapies for ventricular tachycardia.

Besides indicating the existence of a powerful new technique for investigating ventricular tachycardia, the ability to alter the direction and location of the figure-eight reentry circuit also has significance for understanding the mechanism of ventricular tachycardia. Until recently, the reentrant activation sequence was believed always to be a function principally of the electrophysiological characteristics of the tissue.4,31–35 For example, conduction block leading to reentry was thought to occur where a particular degree of dispersion of refractoriness was located or a certain relation between the direction of propagation and tissue anisotropy occurred.32,33

The results of this study suggest that conduction block leading to reentry can occur by a different mechanism that does not require preexisting abnormalities of refractoriness or a particular distribution of intrinsic anisotropic properties of the tissue. This new mechanism is the same as that recently shown by...
Chen and Frazier and coworkers to be responsible for the induction of fibrillation in the normal heart by a large premature S2 stimulus given to a different site than S1 stimulation. In those cases also, the location and direction of the initial cycles of figure-eight reentry are not determined primarily by inhomogeneities of the electrophysiological properties of the myocardium. Instead, a reentrant activation front arises in a region where a certain critical value of the S2 potential gradient field intersects a certain critical degree of refractoriness (Figure 14) to form a critical point. The critical point is thought to lie on the border of the tissue directly excited by the S2 electric field. An activation front propagates away from the border of the directly excited region where the S2 potential gradient is less than the critical point value but not where the gradient is greater than this value. This activation front forms a reentrant circuit with the critical point at its center.

The critical point theory explains why changing the S1 pacing site, the S1S2 interval, or the strength of the S2 will change the activation patterns of reentry and why initial activation sites may be seen at a distance from the S2 stimulation site. For example, changing the S1 site will change the area initially recovered and thus the area initially recovered by the time the S2 stimulus arrives (Figure 14). Similarly, changing the S2 stimulus strength will change the location of the critical point. Increasing the S2 strength will increase the region that is directly excited by the S2 stimulus. This will increase the distance from the S2 site at which the critical potential gradient intersects the critical degree of refractoriness forming a critical point. Hence, earliest activation after the S2 stimulus appears distant from the S2 electrode, at the portion of the border of the directly excited region where the potential gradient was less than the critical value. Chen et al. showed that when S1 and S2 stimuli are given from two point electrodes a few centimeters apart, two critical points are formed. Two reentrant waveforms are thus formed: one centered around each critical point, which together form a figure-eight reentry pattern with the direction of activation in the central part of the pathway directed toward the S1 that was the initial area activated and thus the initial area to recover from refractoriness. These findings...
were predicted by Winfree,\textsuperscript{37} who hypothesized that the ventricular response to strong stimulation could be described by a nonlinear dynamic system with two phases (S\textsubscript{2} strength and tissue refractoriness), and that the heart would respond in a manner similar to some other two-phase nonlinear dynamic systems.

The ability to change the location and direction of the figure-eight reentry during ventricular tachycardia in the present study suggests that the critical point mechanism pertains to the initiation of ventricular tachycardia as well as ventricular fibrillation. This is not to imply that preexisting properties of the tissue do not have a role in reentry during ventricular tachycardia observed in this study. It is evident from Figure 11A that in some areas, preexisting tissue abnormalities do exist, as demonstrated by the area of block present during the S\textsubscript{1} train delivered from the posterior left ventricle. These local tissue abnormalities may also explain the difference in total activation time observed for different S\textsubscript{1} pacing sites. These tissue electrophysiological inhomogeneities may explain why the reentrant pathways changed for several cycles before stabilizing and why the center of the stable reentrant pathways were not always at sites exposed to the precise same S\textsubscript{2} potential gradient level. Thus, both the critical point and the electrophysiological tissue inhomogeneities acting in concert may be important determinants for the sequence of activation during the initiation of ventricular tachycardia by large premature stimuli.

**Clinical Relevance**

Several additional questions must be answered before it can be decided whether the large S\textsubscript{2} technique will be useful for the induction of ventricular tachycardia in patients. It should be determined whether a large premature S\textsubscript{2} stimulus administered to the spared endocardium beneath old infarct scars will induce ventricular tachycardia. If so, the sensitivity and specificity of the technique for inducing the patient’s spontaneous clinical tachycardia must be evaluated because it is possible that the large S\textsubscript{2} will initiate tachycardias that do not occur spontaneously.

The present study confirms and strengthens previous findings that the ECG is insensitive for the detection of the reproducibility of ventricular tachycardia activation patterns and the localization of a particular reentry pathway.\textsuperscript{38,39} These findings suggest that the ECG is determined primarily by large activation fronts spreading away from the infarct site rather than small activation fronts in the spared tissue at the infarct site. This result is concordant with the finding of Josephson et al.\textsuperscript{39} that pacing at different sites during pace mapping can result in similar electrocardiographic configurations for each site. A limitation of this result is that only the three limb leads were examined, and the chest was open at

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**Figure 12.** Mapping. Panels A and B show the figure-eight activation sequence of the seventh and eighth beats, respectively, of a ventricular tachycardia induced by a 30-mA S\textsubscript{2} at an S\textsubscript{1}S\textsubscript{2} interval of 230 msec after an S\textsubscript{1}S\textsubscript{2} train at cycle length 300 msec in a different animal from Figures 2–11. Panel C shows the lead II rhythm strip of the ventricular tachycardia. Panels D and E show the figure-eight activation sequence of the seventh and eighth beats, respectively, of the ventricular tachycardia induced by repeating the same stimulation protocol. Activation sequences induced during both episodes of the arrhythmia are similar. Panel F shows lead II rhythm strip of the ventricular tachycardia induced by repetition of stimulation protocol.
the time of recording. If also true for all 12 leads when the chest is closed, these findings have clinical relevance for the investigation and treatment of patients with ventricular tachycardia, in which specificity depends on induction and recognition of the same ventricular tachycardia that the patient develops spontaneously.

The findings of the present study could explain why the success rate for catheter ablation of ventricular tachycardia is only about 50%. The site of delivery of the shock is determined primarily on the basis of 1) the earliest endocardial activation during the patient’s clinical ventricular tachycardia, 2) the zone of slow conduction as determined by transient entrainment during ventricular tachycardia, and 3) pace mapping. There are at least two general reasons why these ablation techniques may fail. The first reason is that the ablative lesion is created in the wrong location. This could occur because of the insensitivity of the ECG to detect some differences in activation sequences in the thin rim of spared tissue. Thus, the ECG during the arrhythmia induced by programmed stimulation may resemble the ECG during the patient’s clinical arrhythmia, yet the reentry circuit may be in a slightly different location. The second possible reason is that the ablative lesion is too small, because arrhythmias may arise from several sites within the thin rim of spared tissue. The results of this study raise the possibility that many patients do not have a single clinical arrhythmia. Instead, they may have several possible reentry pathways in the peri-infarct tissue that all generate similar patterns in the ECG. A single ablative lesion may eradicate one of the pathways but leave the others intact. Although this concept is highly speculative because we do not know whether the described stimulation technique reproduces spontaneously occurring tachycardia or initiates nonclinical arrhythmias, it does suggest that most of the thin rim of spared tissue should be ablated, as is accomplished surgically by endocardial resection.

Conclusions

This study shows that a strong, premature stimulus administered in the vulnerable period over the epicardium of a 4-day-old infarct may induce either ventricular fibrillation or ventricular tachycardia with a figure-eight reentry pattern. The thicker the trans-
mural extent of infarction and thus the thinner the spared rim of myocardium, the more likely a figure-eight reentry pattern with a longer cycle length will be induced by the $S_2$ stimulus, resulting in ventricular tachycardia rather than ventricular fibrillation. This model for the induction of ventricular tachycardia is advantageous in that the frequency of induction of the arrhythmia is high. As well, the approximate site and direction of activation of the induced rhythm can be predicted in advance, making this a useful model for further investigation and therapeutic manipulation of this arrhythmia. This study has clinical relevance in that it suggests the possible insensitivity of the ECG for the detection of ventricular activation patterns. Thus, multiple reentrant ventricular activation patterns manifesting the same ECG morphology may be present in patients with ventricular tachycardia.

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References

FIGURE 14. Schematic representation of the hypothesized critical point mechanism of the electrical induction of reentry. Panel A shows an idealized strength–interval curve for the response of cardiac tissue to a large premature stimulus given through an $S_2$ electrode several millimeters or more away. The vertical axis indicates the strength of the $S_2$ potential gradient field; $0$, weakest field; 10, strongest field. Horizontal axis represents degree of recovery of tissue after $S_1$ stimulation at the time the $S_2$ stimulus is delivered. $A$, most recovered tissue; $I$, least recovered tissue. Stippling indicates tissue that has recovered enough after $S_1$ stimulation to allow direct excitation by $S_2$ stimulus. White area indicates tissue that is not excited, most of which is still absolutely refractory after $S_1$ stimulation and thus is unaffected by $S_2$ stimulus. However, as this area recovers with time after $S_2$ stimulation, activation fronts arising from tissue directly excited by $S_2$ stimulus can conduct into it. Hatched area indicates tissue in which the cells are at a stage of recovery that results in a graded response and prolongation of repolarization in response to a large $S_2$ stimulus. Activation fronts arising from directly excited tissue cannot conduct into the area in which a graded response and prolongation of repolarization has occurred, yet activation fronts can propagate away from the border of the directly excited region exposed to $S_2$ potential gradients not strong enough to cause a graded response (gradients below the arrow). Whenever a stimulus whose potential gradient field is dispersed to have values that span the critical value shown by the horizontal location of the arrow is applied to tissue whose refractoriness is dispersed to span the critical value shown by the horizontal location of the arrow, an activation front will propagate away from the portion of the border of the directly excited tissue exposed to an $S_2$ potential gradient less than the critical value but will not propagate away from the portion of the directly excited border exposed to a potential gradient greater than the critical value. The activation front will then spiral around the critical point at the arrow, causing a rotor of reentry. In panel B, $S_2$ is delivered from the left side of the plaque and $S_1$ from the center of the plaque. The vertical lines represent the degree of recovery after $S_1$ stimulation at the time $S_2$ is delivered. $A$, most recovered area; $I$, least recovered area. Elliptical lines represent $S_2$ field strength. The strongest field is at the center of the ellipse and the weakest field is at the periphery. Isogradient values 1–6 are labeled, but higher isogradient lines are not labeled because they are spaced so closely together at the center of the panel. Stippled area indicates the tissue directly excited by the $S_2$ stimulus as derived from the strength–interval plot in panel A. Hatched area indicates where graded responses occur. White area indicates tissue absolutely refractory to $S_2$ stimulation plus tissue in which the $S_2$ potential gradient is less than stimulation threshold. As a consequence of this stimulation protocol, two critical points are formed (arrows). Panel C shows an activation front conducting away from the directly excited area into the tissue that was refractory to $S_2$ stimulation and where the $S_2$ gradient was less than the critical point value. Twenty-millisecond isochronal lines are shown. Solid black lines indicate an area of block at the border of the area in which a graded response occurred. Two reentry rotors (one at each critical point) arise, forming the first cycle of a figure-eight reentry pattern. Panels D and E are identical to panels B and C, respectively, with the exception that $S_2$ is delivered from the right side of the plaque so that dispersion of refractoriness is reversed. As a result, tissue directly excited by the $S_2$ stimulus occurs at the right side of the plaque rather than on the left as occurred when $S_1$ was delivered from the left side of the plaque. Consequently, activation sequence is altered, with figure-eight reentry occurring in the opposite direction to that shown in panel C.


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High-current stimuli to the spared epicardium of a large infarct induce ventricular tachycardia.

K M Kavanagh, J S Kabas, D L Rollins, S B Melnick, W M Smith and R E Ideker

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