Vulnerability of the Mildly Ischemic Ventricle to Cathodal, Anodal, and Bipolar Stimulation

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SUMMARY. We studied the difference between myocardial vulnerability to arrhythmias caused by cathodal, anodal, and bipolar stimulation in 29 dogs with partial right coronary artery occlusion. We used 2-msec duration stimuli of up to 8 mA to determine the ventricular vulnerable periods, their relationship to the refractory periods, and the fibrillation or multiple response thresholds for unipolar anodal and cathodal stimulation after two premature ventricular contractions. The vulnerable period for arrhythmias began at the end of the respective refractory periods and terminated at a specific time within the cardiac cycle. Within this period the arrhythmia and excitation thresholds were equal. Because shorter refractory periods were obtained with anodal stimulation than cathodal, the vulnerable periods for anodal stimulation were longer. This indicated that the vulnerable periods for bipolar stimulation also would be longer than for unipolar cathodal stimulation since bipolar and anodal refractory periods are equal when the cathode and anode are of similar surface area. Results from seven of the experiments showed that a dual focus of excitation, which can only occur with bipolar stimulation, did not make the ventricle more vulnerable to arrhythmias than did unipolar stimulation. These results indicate that the difference between the arrhythmia vulnerability to unipolar cathodal, anodal, and bipolar stimulation is dependent on the relationship between their excitability characteristics, i.e., their strength-interval curves.

THE EXISTENCE of a brief period in the ventricular cycle during which electrical stimulation can induce arrhythmias such as ventricular fibrillation was demonstrated in animals by Wiggers and Wegria, 1 and often has been verified. 2-3 The extensive clinical use of cardiac stimulation has made the circumstances under which such electrical stimulation may cause an arrhythmia of importance. Although most investigations indicate that the minimum energy required to precipitate ventricular fibrillation in the normal myocardium exceeds that delivered by a clinical cardiac pacemaker, there have been clinical reports of ventricular fibrillation and tachycardia associated with a pacemaker stimulus falling in the "vulnerable period" of the cardiac cycle. This suggests the presence of pathophysiological and pharmacological factors that lower the threshold to arrhythmias such as myocardial ischemia, sympathetic activity, and premature ventricular beats. 4-6 Aside from these factors, the effects of electrode and stimulus characteristics on myocardial vulnerability are not yet well understood.

A recent analysis of cases of ventricular fibrillation and tachycardia attributed to pacemaker stimuli found that most such arrhythmias arose in patients undergoing bipolar rather than unipolar cathodal stimulation. 7 In our own review of the literature, 8 we found 26 cases in which the initiation of ventricular fibrillation or tachycardia (defined as at least a run of 3 premature ventricular contractions) was illustrated. In all of the 22 cases in which the mode of stimulation was mentioned, it was bipolar. This suggests that there is a difference between myocardial vulnerability to unipolar cathodal and to bipolar stimulation and its assessment was thus undertaken in studies on the canine ventricle.

The term bipolar stimulation refers to a configuration of electrodes in which both the cathode and the anode are in contact with the myocardium. Excitation can then be elicited from the cathode, the anode, or from both sites simultaneously, depending upon the strength of the bipolar stimulus and its timing in the cardiac cycle. 9-10 When the cathode and the anode are of almost equal surface area, a bipolar stimulus of strength close to threshold causes excitation arising at the cathode during diastole and at the anode during the relative refractory period (Fig. 1). With higher stimulus strengths, excitation arises from both the cathode and the anode during diastole and up to the cathodal relative refractory period. This means that bipolar stimulation may be more likely to cause arrhythmias than unipolar cathodal stimulation either because it can give rise to two simultaneous foci of excitation (bifocal excitation) or because during part of the cardiac cycle bipolar stimulation in fact becomes unipolar anodal stimulation.

In many previous studies of the vulnerable period rather strong stimuli were used to evoke fibrillation. Commercial pacemakers, on the other hand, produce stimuli with an energy level of less than 100 microjoules and it is important to use comparable stimuli to obtain results applicable to the conditions under which pacemaker stimuli induce arrhythmias. However, such low energy stimuli, whether unipolar or bipolar, rarely, if ever, cause arrhythmias when applied to the normal myocardium, no matter when they are applied during the cardiac cycle. In order to create conditions under which such stimuli can cause arrhythmias, we used a preparation in which we caused mild myocardial ischemia and applied the test stimuli after...
inducing two premature impulses in succession. The test stimulus ($S_3$) was, therefore, the third in a series of premature stimuli. By varying the interval at which the test stimulus fell, the recovery of excitability, i.e., the strength-interval curve, was mapped following the second premature impulse; we did this with unipolar anodal and unipolar cathodal stimuli. We also determined the ability of unipolar cathodal and anodal stimuli to produce arrhythmias when applied at various times during the cardiac cycle. In another set of experiments excitation was initiated with unipolar or bipolar stimuli causing two simultaneous foci of excitation and the ability of those stimuli to induce fibrillation when applied after two premature contractions was compared.

**Procedure**

**VULNERABILITY TO UNIPOLAR CATHODAL AND ANODAL STIMULATION**

A right thoracotomy was performed on 22 mongrel dogs weighing 15–25 kg, anesthetized with sodium pentobarbital (30 mg/kg iv), and ventilated with a Bird respirator. The pericardium was opened and used to cradle the heart. The right coronary artery was occluded between the second and third or the third and fourth perforating branches. A unipolar epicardial electrode 2–3 mm² in surface area, made of Elgiloy (Elgin National Watch Company trade name for an alloy of cobalt, iron, chromium, molybdenum, nickel, and manganese), was sutured to the ventricular apex and a bipolar recording electrode was sutured within 1–2 cm of it to record the electrogram. The electrogram and lead 2 of the ECG were displayed simultaneously and recorded. Sinus control of the heart was stopped by clamp that crushed the sinoatrial node and the ventricles were paced at 150 beats/min via the apical electrode. At least 1/2 hour was allowed to elapse before tests were made.

Three stimuli, $S_1$, $S_2$, and $S_3$, were then delivered to the ventricle through the apex electrode after every 75th beat. $S_1$ and $S_2$, which initiated the first two premature ventricular contractions (PVC), were anodal in polarity (chosen arbitrarily), about 4.0 mA in amplitude, and 2 msec in duration. These were applied at a delay of 10–20 msec beyond the refractory period of the previous beats. The anodal or cathodal test stimulus, $S_3$, was applied in the normally excitable period after the second PVC. With $S_1$ and $S_2$ remaining constant in delay and amplitude and $S_3$ set at a fixed delay, the excitation threshold and the minimum cathodal and anodal current required to initiate fibrillation or multiple responses (unstimulated PVC's) were determined by increasing $S_3$ in steps of 0.5 mA to a maximum of 8 mA. The $S_2$ delay was then decreased by 10–20 msec and the stimulation sequence repeated to scan the entire excitable period. When fibrillation or multiple responses could not be initiated at any delay, $S_1$ and $S_2$ were made more premature and the process repeated.

In the experimental setup the basic paced rate of 150 beats/min was set by the pulse generator and the delays of $S_1$, $S_2$, and $S_3$ from the heart rate determining stimulus (S) were manually set on the Digitimer (Devices Sales Ltd., Hertfordshire, England). The constant current output of each isolated stimulator and the polarity and pulse duration (2 msec) were checked by measuring the voltage drop across a 1 ohm resistor connected in series with the stimulating electrode. During the application of the 3 stimuli, and for about a second thereafter, the ventricular pacing stimulus was interrupted by a reed relay to allow the effects of the test stimuli to be monitored. A 'relay driver' kept the relay open for the desired interval after which it closed, and ventricular stimulation resumed at 150 beats/min until the next test cycle.

Ventricular fibrillation could not be precipitated in all the experiments. When fibrillation could not be produced, multiple responses (defined as at least one unstimulated response after the third PVC produced by $S_3$) were considered as the induced arrhythmia. Whenever fibrillation did occur, defibrillation was performed immediately and at least half an hour was allowed for ventricular recovery. When multiple responses occurred, an interval of 5 minutes was sufficient for the recovery of ventricular excitability. To validate reproducibility of data, an attempt was made to repeat each set of parameters yielding multiple responses or fibrillation. In some experiments a few episodes of fibrillation followed by defibrillation occurred before a stable physiological state could be achieved. Immediate defibrillation and careful control of anesthesia
aided reproducibility although the myocardium did not always recover following defibrillation. In such cases the experiment was terminated.

VENTRICULAR VULNERABILITY TO FIBRILLATION WITH SINGLE AND DUAL FOCI OF EXCITATION

Seven dogs were studied with the experimental arrangement described above. A bipolar electrode with stimulation sites 1 cm apart was sutured near the ventricular apex. The basic heart rate stimulus (S), and the first and second premature stimuli (S₁ and S₂) were bipolar. A test pulse S₃, which was either unipolar cathodal, unipolar anodal or bipolar was applied after every 75th beat to induce fibrillation. For unipolar cathodal stimulation the cathodal pole of the bipolar electrode remained negative with the metallic chest retractor acting as the indifferent positive electrode, whereas for unipolar anodal stimulation the anodal part of the bipole was positive and the indifferent electrode negative. The test stimulus (S₃) was applied at different delays after S₂. At each delay and current strength, all three modalities of stimulation were tested with S₁ and S₂ remaining constant in magnitude and pulse duration. The main purpose of this study was to determine if fibrillation could be precipitated by bifocal stimulation and not by unipolar or vice versa. The sequence of unipolar (cathodal and anodal) and bipolar stimulation was reversed alternately and the current strength was increased or decreased in steps of 0.5 mA. Unipolar cathodal and anodal stimulation were followed by bipolar stimulation only after ensuring that the unipolar stimuli were suprathreshold. If fibrillation did not occur at any delay, S₁ and S₂ were made more premature and the process repeated until fibrillation could be induced. Multiple fibrillations and defibrillations were attempted in each animal.

Results

VULNERABILITY TO UNIPOLAR CATHODAL OR ANODAL STIMULATION

The strength interval curve, the vulnerable period, and the threshold for arrhythmias were determined for cathodal and anodal stimuli in 12 dogs. In six dogs it was possible to induce ventricular fibrillation; in the other six the only arrhythmia was multiple response (defined as at least one unstimulated ventricular contraction). In another set of six experiments, the anodal and cathodal fibrillation thresholds were compared only at a single delay.

Experiments in Which Ventricular Fibrillation was Induced

The vulnerable period for fibrillation was defined as the interval after the second PVC during which a suprathreshold stimulus could induce fibrillation. It was found that the vulnerable period for either anodal or cathodal stimuli always ended at the same moment within the cardiac cycle; the vulnerable period began, however, at the end of the absolute refractory period. Since the ventricle can be excited by anodal stimuli earlier than by cathodal stimuli, the vulnerable period to anodal stimuli was longer than to cathodal stimuli. Within the vulnerable period, the excitation and fibrillation thresholds were always equal, i.e., excitation always caused fibrillation. The only difference between the cathodal and anodal effects was the minimum amplitude of the stimulus required to initiate excitation and hence fibrillation. Immediately following the vulnerable period, suprathreshold cathodal and anodal stimuli (up to 8 mA) produced one, two, or three unstimulated PVC's (multiple responses) when applied within an interval which varied between 10-40 msec in the different experiments. The number of unstimulated PVCs evoked by various suprathreshold stimuli was not documented in any single experiment. When the stimulus delay was further increased, multiple responses did not occur at any current strength.

The minimum currents required to produce ventricular fibrillation at various delays in two of the six experiments are illustrated in Figure 2. Since most thresholds were determined twice, the current represents the mean of two threshold measurements. In experiment 2 (Fig. 2A) the
The difference between the ability of cathodal and anodal stimulation to initiate arrhythmias can be compared in two ways; the first is the ratio of cathodal and anodal fibrillation thresholds at each delay within the vulnerable period. The cathodal arrhythmia threshold always was greater than the anodal threshold, but the ratio was determined in the early part of the vulnerable period because the maximum current strength had been limited to 8 mA. The second parameter is the difference in duration of the anodal and cathodal vulnerable periods at each current strength. Both vulnerable periods decreased in duration with decreasing current strength, but the anodal vulnerable period was always longer than cathodal. Therefore, at any given current strength, an anodal stimulus could initiate an arrhythmia over a longer period than could the cathodal stimulus. This difference in the length of the vulnerable period is clinically relevant. Should pacemaker stimuli become competitive with spontaneous activity and thereby fall at random during the cardiac cycle, an anodal stimulus would have a greater possibility of initiating ventricular fibrillation because it can initiate fibrillation both at a lower strength and during a longer period of the cardiac cycle. In the present studies, the anodal vulnerable period was longer than the cathodal by a maximum of 24 msec (Table 1). The difference generally increased as the stimulus strength decreased. Therefore, at low stimulus strengths, though the vulnerable period was short, the myocardium was more susceptible to induction of arrhythmia by anodal than cathodal stimulation. No significant correlation was found between the duration of the anodal vulnerable period at 8 mA, the difference between the cathodal and anodal vulnerable periods and the parameters $t_1$ and $t_2$ (Table 2). These results were in agreement with the data obtained in studies in which the complete vulnerable period was determined in the early part of the vulnerable period because irreversible ventricular fibrillation, cathodal and anodal fibrillation thresholds were measured at least at one delay. These results were in agreement with the data obtained in studies in which the complete vulnerable period was determined. In the relative refractory period the cathodal fibrillation thresholds were consistently higher than anodal by a factor of 1.3 to 3.1.

### Table 1 Results of Experiments in Which the Complete Vulnerable Period (VP) for Ventricular Fibrillation was Determined

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Anodal VP-Cathodal VP (msec)</th>
<th>$t_1$ (msec)</th>
<th>$t_2$ (msec)</th>
<th>$t_2$/400</th>
<th>Anodal VP - 8 mA (msec)</th>
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<tr>
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<td>10</td>
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<td>80</td>
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</tr>
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<td>2</td>
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<td>6</td>
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<td>5</td>
<td>6</td>
<td>5</td>
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$t_1$ = delay of $S_1$ from the previous heart rate stimulus $S$. $t_2$ = delay of $S_2$ from $S_1$. 

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**Figure 3** Myocardial vulnerability to fibrillation with cathodal and anodal stimuli after two PVC's (experiment 5). In each strip, Lead II of the ECG is shown at the top and the local electrogram at the bottom. The three arrows show the timing of $S_1$, $S_2$, and $S_3$. Downward pointing arrows indicate cathodal stimuli and upward arrows indicate anodal stimuli. The two PVC's are elicited by $S_1$ and $S_2$ which are delayed by 200 and 350 msec, respectively, from the previous heart rate determining stimulus. (A) a 1.0 mA cathodal test stimulus ($S_3$) at a delay of 120 msec from $S_2$ does not elicit excitation. (B) a 1.0-mA anodal test stimulus at the same delay initiates excitation precipitating fibrillation. (C) at the delay of 120 msec, a minimum cathodal stimulus of 3.0 mA is required to initiate excitation and hence fibrillation. When the experiments in B and C are repeated, the anodal and cathodal excitation and fibrillation thresholds are 1.5 and 2.5 mA, resulting in average thresholds of 1.25 and 2.75 mA, respectively, as indicated in Figure 2B. At an increased delay of 170 msec suprathreshold anodal (D) and cathodal (E) stimuli of 4.0 mA do not precipitate fibrillation and hence are outside the vulnerable period. (Note: The strips were retouched for illustrative purposes.)
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Table 2

Results of Experiments in Which Cathodal (C) and Anodal (A) Fibrillation Thresholds by Test Stimuli were Determined Only at One Interval in the Cardiac Cycle

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>t1 (msec)</th>
<th>t2 (msec)</th>
<th>t3 (msec)</th>
<th>t3/400</th>
<th>t3/t1</th>
<th>Fibrillation threshold (mA)</th>
<th>A/C fibrillation threshold</th>
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<tr>
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<td>150</td>
<td>100</td>
<td>0.43</td>
<td>0.88</td>
<td>5.50</td>
<td>1.75</td>
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</table>


Table 2: Results of Experiments in Which Cathodal (C) and Anodal (A) Fibrillation Thresholds by Test Stimuli were Determined Only at One Interval in the Cardiac Cycle

Experiments in Which Only Multiple Responses were Induced

In six experiments the only arrhythmic activity observed was unstimulated PVC's (multiple responses) and fibrillation could not be induced even with the most premature stimuli. Again, in all the experiments the excitation and arrhythmia thresholds were equal throughout the vulnerable period for multiple responses and the anodal and cathodal vulnerable periods terminated simultaneously (Fig. 4). In the succeeding nonvulnerable period only single stimulated premature beats occurred even with suprathreshold stimuli. The pattern of the arrhythmia within the vulnerable period was, however, not the same in all the experiments. In one experiment (8), a single unstimulated PVC was produced with currents up to 8 mA. In three other experiments (7, 9, and 10) two unstimulated PVC's followed stimulation early in the vulnerable period whereas only one PVC occurred later in the vulnerable period. In two additional experiments (11 and 12), two consecutive applications of premature stimuli of any amplitude could produce one, two, or three unstimulated PVC's at any time in the vulnerable period. The demarcation between the vulnerable and nonvulnerable periods, however, was distinct.

In all experiments the anodal vulnerable period for multiple responses was longer than or equal to the cathodal period (Table 3). There was no significant correlation between the duration of the anodal vulnerable period at 8 mA, the difference between the cathodal and anodal vulnerable periods, and the time delays of S1, S2, or their ratio.

Vulnerability to Arrhythmias with Single and Dual Foci of Excitation

Thirty-three episodes of ventricular fibrillation were documented in seven dogs. None occurred preferentially with unifocal or bifocal stimulation. A bifocal stimulus never initiated arrhythmias when suprathreshold unipolar cathodal and anodal stimuli of the same strength and at the same interval failed to do so. Similarly, a unipolar stimulus never initiated an arrhythmia after a bipolar stimulus was ineffective in doing so. All arrhythmias occurred with the initial application of a single unipolar or bipolar stimulus within the vulnerable period. Among the 33 cases of ventricular fibrillation, 18 occurred with unipolar anodal or cathodal stimulation and 15 with bipolar stimulation, a difference not statistically significant. Therefore, a dual focus of excitation did not increase or decrease myocardial arrhythmia susceptibility.

Discussion

These experiments help to explain the difference in myocardial vulnerability to cathodal, anodal, and bipolar stimulation. The results indicate that in the ischemic myocardium, arrhythmias can be evoked after premature contractions when suprathreshold stimuli fall within a vulnerable period which begins at the end of the absolute refractory period and extends for part of the cardiac cycle. The cardiac response is not significantly influenced by the strength of a suprathreshold stimulus (up to 8 mA at 2 msec pulse duration) but differs in different portions of the cardiac cycle. Depending upon the state of the myocardium, one of three conditions can occur. There can be a vulnerable period for fibrillation followed by another in which multiple responses occur. It is important to note that this sequence of vulnerable periods was never reversed in our experiments. It is also possible that only a
vulnerable period for multiple responses may be present. Third, there may be no vulnerable period for stimuli 2 msec in duration and up to 8 mA in strength so that only single stimulated responses occur throughout the excitable period of the cardiac cycle.

The difference in vulnerability to cathodal and anodal stimulation is a result of certain characteristics of cardiac excitability. Since the absolute refractory period is shorter for anodal stimuli than for cathodal at most current strengths, the vulnerable period for anodal stimulation is longer. This relationship is depicted in Figure 5A in which the end of the vulnerable period is labeled T1. Here the difference between the cathodal and anodal refractory periods will equal the difference in the vulnerable periods except in the region of the anodal "dip." However, it is also possible to have a short vulnerable period extending until T2 (Fig. 5B) in which case only an anodal supra-threshold stimulus will precipitate arrhythmias. The anodal dip of Figure 5 is often observed after a paced or a conducted beat but was absent in most of our experimental results. This could be because the stimulus intensities were increased in steps of 0.5 mA and masked the dip region or because the dip may not be present following successive PVCs.

In order to make a more general comparison of myocardial vulnerability to cathodal and anodal stimuli it is important to determine whether the cathodal and anodal strength-interval curves are similar under different circumstances. Although the present set of measurements were made after two PVC's, the refractory period to anodal stimuli is shorter than the refractory period to cathodal stimuli in the normal or ischemic paced ventricle, during atrial pacing and following a single premature ventricular contraction. Therefore, if the factors responsible for the arrhythmias remain the same as those occurring in the present experiments, one would expect to observe lower arrhythmia thresholds for anodal than for cathodal stimulation. An example of this in a paced ischemic canine ventricle is given in Figure 6. Here a 7-mA (2 msec) cathodal stimulus at a delay of 212 msec falls in the refractory period whereas a similar anodal stimulus at the same delay initiates a contraction and fibrillation. It is important to note that our studies were conducted during acute myocardial ischemia. The electrophysiological factors for the genesis of ventricular arrhythmias during chronic ischemia may not be the same and may alter the relationship between vulnerable and refractory periods.

These experiments also help explain the difference between myocardial vulnerability to arrhythmias with cathodal and bipolar stimulation. The bipolar excitation threshold at any time during the cardiac cycle is equal to the lower of the unipolar cathodal and anodal thresholds as determined at the respective negative and positive sites.

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**TABLE 3** Results of Experiments in Which the Vulnerable Period (VP) for Multiple Responses was Determined

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>8 mA</th>
<th>7 mA</th>
<th>6 mA</th>
<th>5 mA</th>
<th>4 mA</th>
<th>3 mA</th>
<th>2 mA</th>
<th>t1 (msec)</th>
<th>t2 (msec)</th>
<th>t1/400</th>
<th>t2/t1</th>
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<td>7</td>
<td>18</td>
<td>22</td>
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<td>0.07</td>
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</table>

\( t_1 = \) delay of \( S_1 \) from \( S_2 \); \( t_2 = \) delay of \( S_2 \) from \( S_1 \).

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**FIGURE 5** Possible relationships between cathodal and anodal strength-interval curves and the vulnerable period for arrhythmias. In A, the vulnerable period extends up to \( T_1 \), and in B, up to \( T_2 \). See text for discussion. Oblique lines indicate vulnerable ranges for cathodal (///) and anodal (\\) stimuli.

**FIGURE 6** Difference between the vulnerability of a paced ischemic ventricle to a cathodal and anodal stimulus. (A) a 7.0-mA cathodal stimulus at a delay of 212 msec after the pacing stimulus fails in the refractory period. (B) a 7.0-mA anodal stimulus at the same delay initiates excitation which precipitates fibrillation.
of a bipolar electrode (Fig. 1). With threshold bipolar stimuli, if the anodal and cathodal electrodes are of equal surface area excitation normally originates from the anode in the relative refractory period and from the cathode during diastole. This means that the refractory period to anodal and bipolar stimuli is the same. Therefore, in an arrhythmia prone ventricle, the respective vulnerable periods would also be equal and both would be longer than for unipolar cathodal stimulation. This relationship between cathodal, anodal, and bipolar refractory periods can, however, alter when the surface areas of the anode and cathode are dissimilar since it is the current density that primarily determines excitation threshold. It has been suggested that the two foci of excitation, which occur when the bipolar stimulus is above the unipolar cathodal and anodal thresholds, also may facilitate ventricular arrhythmias because of interaction between the two wavefronts. Our results with low energy stimulation do not support such a contention. Comparison of unipolar and bifocal stimulation did not reveal any cases in which fibrillation could be induced by a bifocal stimulus and not by an equal unipolar stimulus at the same period of the cardiac cycle.

Methods other than those used in this study have been used in the past to compare myocardial vulnerability to arrhythmias during the different modes of stimulation. Harris and Moe in 1942 used DC currents of 3-4 seconds duration on the canine ventricle and found that the anodal fibrillation threshold was considerably lower than cathodal. Comparison of cathodal, anodal, and bipolar fibrillation thresholds by 100 Hz train stimulation show anodal and bipolar thresholds to be equal and considerably lower than the cathodal threshold. All these results can be explained by the fact that the anodal or bipolar stimulus that initiated fibrillation could excite more prematurely than could a cathodal stimulus of the same current strength. However, there are certain drawbacks to this technique which have recently been investigated. One of the problems associated with using trains of stimuli is that anodal stimuli placed in the absolute refractory period could excite more prematurely than could a cathodal stimulus of the same current strength. This would heighten the disparity of cathodal and anodal refractory periods and hence the use of trains of stimuli, if the anodal and cathodal electrodes are of equal size, may facilitate ventricular arrhythmias because of interaction between the two wavefronts. Our results with low energy stimulation do not support such a contention. Comparison of unipolar and bifocal stimulation did not reveal any cases in which fibrillation could be induced by a bifocal stimulus and not by an equal unipolar stimulus at the same period of the cardiac cycle.

The results of our investigation are supported by clinical observations. The relationship between closely coupled premature beats and arrhythmias has been emphasized by the experience gained in coronary care units. In 26 cases of pacemaker-induced ventricular fibrillation or tachycardia, with its initiation documented by ECG, the pacer stimulus that originated the arrhythmia fell on the T wave. The case of Bilitch et al. demonstrates the relationship between the vulnerable and the refractory periods during low energy stimulation. In this patient, runs of ventricular tachycardia and fibrillation were caused by a 2 mA, 2 msec stimulus. The vulnerable period, during which the pacemaker stimuli initiated the arrhythmia, was about 20 msec in duration and began at the end of the refractory period. In vitro studies also have shown that rapid activity in cardiac fibers can be induced only by early conducted beats and not by later ones. The relationship between the vulnerable period and the strength-interval curve determined by our studies and observed by Bilitch differs from those obtained by other investigators who utilized much higher energy stimuli to initiate arrhythmias in nonischemic hearts. In those experiments the fibrillation threshold during the vulnerable period was many times greater than the excitation threshold within that period. This observation has been explained on the basis that the temporal dispersion of the recovery of excitability increases with increasing stimulus strength and therefore, in a normal myocardium, high energy stimuli were required to develop sufficient myocardial inhomogeneity to result in fibrillation. In our experiments, threshold stimuli were adequate to cause fibrillation presumably because the electrophysiological inhomogeneity of the myocardium was augmented by ischemia and PVC's rather than by strong stimuli. A more striking discrepancy is that if high energy bipolar stimuli are applied to a nonischemic myocardium, the vulnerable period does not start at the termination of bipolar refractory period but after a short interval following the absolute refractory period. In the present experiments the ischemic tissue and the premature beats may have been responsible for increasing the duration of the vulnerable period so that it started at the termination of the absolute refractory period. We consider this to be a situation which more closely resembles that under which cardiac pacemakers may initiate arrhythmias.

The electrophysiological basis of the vulnerable period in these acute experiments can be derived from our present understanding of arrhythmias. Among the factors that facilitate arrhythmias, such as ventricular fibrillation, are increased dispersion of refractory periods, decreased conduction velocity and shorter refractory periods. All these factors favor re-entry and are heightened by increasing prematurity of suprathreshold stimuli. Premature stimulation may also initiate ventricular fibrillation by triggering automatic focal discharge. In cardiac tissue preparations such triggerable activity has been observed with short coupling of premature stimulation and not with a longer coupling. From a clinical viewpoint, this investigation strengthens the argument that competitive bipolar pacing is more likely to produce arrhythmias than is unipolar cathodal pacing. A detailed clinical study with some of the commercially available electrodes will be presented in a future publication.

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