Initiation of Sustained Ventricular Tachyarrhythmias in a Canine Model of Chronic Myocardial Infarction: Importance of the Site of Stimulation

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SUMMARY The importance of the site of stimulation to the initiation of sustained ventricular tachyarrhythmias was determined in 24 adult mongrel dogs. Studies were performed 3–30 days after two-stage occlusion of the mid- or distal left anterior descending coronary artery, modified by a reperfusion stage. Unipolar cathodal stimuli of threshold intensity and 2 msec duration were introduced at five to 24 sites in each dog in the distribution of occluded and nonoccluded vessels. Strength-interval curves were constructed from 232 measurements at these sites and local properties of excitability and refractoriness were correlated with the ability to initiate arrhythmias. All dogs had sustained ventricular tachyarrhythmias inducible from at least one site. Intramyocardial sites with normal excitability and refractoriness within 2 cm of an area of infarction were most often successful (27 of 44, 61%) in the initiation of sustained arrhythmias. Less successful sites included normal left ventricular plunge electrode sites > 2 cm from an area of infarction (eight of 32, 25%) (p = 0.002), left ventricular plunge electrode sites within an area of infarction (20 of 103, 19%) (p < 0.001), normal right ventricular sites (five of 24, 21%) (p < 0.001), and endocardial catheter sites (six of 29, 21%), (p < 0.001). These findings suggest that local properties of excitability and refractoriness at the site of stimulation, as well as anatomic and geometric factors, may be critical in the initiation of sustained ventricular tachyarrhythmias using the technique of programmed electrical stimulation.

ELECTROPHYSIOLOGIC STUDIES are an important method of determining possible arrhythmic mechanisms and designing effective therapy in patients with recurrent sustained ventricular tachyarrhythmias.1–14 The application of programmed electrical stimulation for these purposes has been based on the premise that the sustained ventricular tachyarrhythmias initiated in the catheterization laboratory relate directly to dysrhythmias that occur clinically.3, 5, 6, 8, 13, 15 In clinical practice, however, electrophysiologic studies have not always been completely successful.3, 5, 6, 12 For, sustained ventricular tachyarrhythmias (i.e., ≥ 1 minute in duration) may have multiple mechanisms, and some dysrhythmias may not be amenable to initiation using routine programmed pacing techniques.3, 5, 8, 17 In addition, the methods of programmed electrical stimulation (i.e., the introduction of one or multiple ventricular extrastimuli during a spontaneous or paced rhythm) are not necessarily performed in an identical manner. Electrophysiologic studies may vary with respect to the use of right vs left ventricular stimulation,8, 13 the number of sites from which arrhythmia initiation is attempted,8, 13 in the use of multiple paced cycle lengths,3, 5, 6, 12 and in the use of adjunctive interventions, such as isoproterenol administration.8, 17

In recently developed canine models of chronic myocardial infarction,18–21 dogs studied at least 3 days after two-stage occlusion of the left anterior descending coronary artery, modified by a reperfusion stage, have been shown to be susceptible to the reproducible initiation of sustained ventricular tachyarrhythmias using methods of programmed electrical stimulation comparable to those performed routinely in the clinical electrophysiologic laboratory. The tachyarrhythmias initiated in these canine models are also similar to those induced in man in the clinical laboratory.20, 21 In the present study we evaluated the importance of the site of stimulation to the initiation of sustained ventricular tachyarrhythmias using an experimental canine model of chronic myocardial infarction.21

Materials and Methods

Studies were performed on 24 healthy adult mongrel dogs that weighed 8–16 kg. The dogs were anesthetized with i.v. sodium pentobarbital (30 mg/kg) and then ventilated with room air through a cuffed pharyngeal-branch tube using a volume-cycled positive-pressure respirator. Body temperature was maintained with a thermal mattress. Using routine surgical procedures, the heart was exposed through a limited (< 4 cm) left thoracotomy at the fourth left intercostal space, the pericardium opened and a pericardial sling created. All dogs underwent two-stage occlusion of the mid- or distal left anterior descending coronary artery, followed by reperfusion after 2 hours of complete occlusion. Reestablishment of pulsatile arterial blood flow distal to the site of occlusion was evident in each case. Five minutes before release, dogs were pretreated with a bolus of i.v.
lidocaine, 2 mg/kg, and 5 minutes after release with a second lidocaine bolus (1 mg/kg). There were no episodes of ventricular fibrillation associated with release in dogs pretreated in this manner.

The chests were closed and routine postoperative care was administered, including prophylactic antibiotic therapy (either penicillin or cefazolin plus streptomycin, both intramuscularly). At 3–30 days after initial occlusion, when the dogs were otherwise clinically stable, and the accelerated ventricular arrhythmias of the first 24–48 hours had subsided, dogs were anesthetized with i.v. sodium pentobarbital (10–20 mg/kg) plus diazepam (1–2 mg/kg), or pentobarbital, 30 mg/kg. Ventilation and body temperature were maintained as above, and the heart was exposed via a left lateral thoracotomy. Using 22-gauge needles, Teflon-coated stainless steel, bipolar plunge (hook) wire electrodes (0.1 mm diameter) were placed in multiple subepicardial, intramyocardial and subendocardial sites within areas in the distribution of both occluded and nonoccluded vessels. The plunge electrodes were insulated except at the tip. Rectangular cathodal current pulses 2 msec in duration were delivered by a constant current source, which was continuously variable from 0–10 mA. The indifferent anode was a stainless steel rib speader with an approximately 8-cm² surface in contact with the chest wall. Programmed electrical stimulation was performed using a custom-designed digital stimulator (Bloom Associates, Ltd.). In selected experiments, right and/or left ventricular multipolar electrode catheters with 1-cm interelectrode distances were introduced by cutdown via the jugular or carotid vessels to evaluate arrhythmia initiation using endocardial catheter stimulation. For the purpose of this study, endocardial catheter sites of stimulation were limited to those with normal diastolic excitability thresholds. Using unipolar cathodal current and pacing from the electrode at the tip of the catheter, this threshold was always < 0.60 mA.

Dogs were evaluated initially to confirm their susceptibility to sustained ventricular tachyarrhythmias. Using unipolar cathodal stimulation with twice-diastolic-excitability-threshold current, simultaneous ventricular and atrial pacing was done at a cycle length of 300 msec, and ventricular extrastimuli were introduced after every eighth drive beat. In selected dogs, additional studies were also done to evaluate the effects of using five-times-threshold extrastimuli during drive pacing at twice-threshold intensity. All 24 dogs included in this analysis had sustained ventricular tachyarrhythmias inducible reproducibly from at least one site with either one (seven dogs), two (10 dogs) or three (seven dogs) ventricular extrastimuli using twice-threshold current. Sustained ventricular tachyarrhythmias were defined as non-self-terminating (> 1 minute) ventricular tachycardia (cycle length ≥ 120 msec, 12 dogs), ventricular flutter (cycle length 100–120 msec, regular, five dogs), or ventricular fibrillation (seven dogs). In selected experiments, arrhythmia initiation was also attempted during drive pacing at cycle lengths of 500 msec and 220 msec. In addition to the 24 dogs in this study, five others were also evaluated: three sham-operated controls and two study dogs did not have inducible arrhythmias with either programmed pacing or with bursts of rapid ventricular pacing (cycle length 120–150 msec). These five dogs were not included in the statistical analysis of the importance of the site of stimulation.

Measurements of Excitability and Refractoriness

Thresholds for excitability were determined at each electrode site using unipolar cathodal stimulation. Strength-interval curves were constructed by the following method: An extrastimulus (S₂) was introduced in late diastole at the minimum milliamperage for eliciting a ventricular response (Vₙ) after eight ventricular drive beats at a basic cycle length of 300 msec. In dogs with less than 1:1 retrograde ventriculo-atrial conduction during ventricular drive pacing, left atrial pacing was done simultaneously with ventricular drive pacing to prevent interference by supraventricular capture beats. The current for the drive beats was held constant throughout the determination at twice the minimum diastolic threshold for excitability. The coupling interval of S₂ was then decreased in 1–2-msec steps until S₂ failed to elicit a Vₙ. When S₂ failed to elicit a Vₙ, the milliamperage of S₂ was then increased incrementally until a Vₙ was elicited, and the coupling interval decreased until S₂ again failed to elicit a Vₙ. This sequence was repeated until an effective refractory period (ERP) was reached at a maximum current of 10 mA. The ERP, therefore, was defined at the longest SₙS₂ interval that failed to elicit a Vₙ at 10 mA. To verify their configuration and reproducibility, strength-interval curves were also constructed at representative sites using a second method. The minimum milliamperage required to elicit a response at each of multiple coupling intervals in diastole was determined independently rather than shortening the coupling interval to refractoriness at each given current intensity. This was done by first setting the coupling interval for S₂ and increasing the current from 0 to the minimum current required for eliciting a Vₙ at that coupling interval. This method also facilitated construction of strength-interval curves at sites where single ventricular extrastimuli initiated ventricular tachyarrhythmias. Unipolar cathodal stimulation was done to avoid the complex strength-interval relations that characterize both unipolar anodal and bipolar stimulation.

The relative refractory period (RRP) was defined as the longest coupling interval along the strength-interval curve at which the current required to evoke a response (Vₙ) increased above the diastolic excitability threshold by greater than 0.10 mA for a ≤ 4-msec change in coupling interval. This criterion was chosen to provide adequate resolution and consistency in determining the longest coupling interval that showed an increased threshold current requirement for stimulation. For the purpose of this study, the ventricular refractory period (VRP) was defined as the
refractory period (longest S1S2 not eliciting a response) for the ventricular extrastimulus measured at exactly twice the diastolic excitability threshold for that site. Properties of threshold for excitability (i.e., minimum current consistently eliciting a V1 at a long diastolic coupling interval), ERP, RR and VRP at twice-diastolic-excitability threshold were determined for multiple subendocardial, intramyocardial and subepicardial sites from within the area of infarction and from multiple sites within normal control areas in each dog. The limit of resolution of refractory-period measurements was within ± 1 msec. Electrophysiological properties at multiple sites, as well as the ability to initiate sustained ventricular tachyarrhythmias, were reevaluated throughout the study, both before and after all interventions (including countershock) to validate the stability of results at different sites over time. Measurements of refractory periods remained stable within ± 1 msec and excitability thresholds remained stable within ± 0.02 mA over the course of each experiment.

**Postmortem Examination**

After electrophysiologic studies were completed, dogs were sacrificed with plunge electrodes left in situ, and each plunge electrode position was confirmed at postmortem examination using 1-2 mm-thick slices of myocardium. Hearts were then thinly sectioned and histopathologic studies were done using either hematoxylin-eosin, trichrome or nitroblue tetrazolium staining. Histopathologic findings were then correlated with local electrophysiologic properties.

All experiments conformed to the "Guiding Principles in the Care and Use of Animals" approved by the Council of the American Physiological Society and to the Animal Care Policies of the University of Pennsylvania and Lankenau Hospital.

**Statistical Methods**

Data were subjected to chi-square analysis to test whether left ventricular plunge electrode sites within 2 cm of the edge of an area of infarction were most successful in initiating ventricular tachyarrhythmias. The degree of success for the <2-cm sites was compared to that for each of four other sites using a chi-square test. These other sites included: normal left ventricular plunge electrode sites > 2 cm from the edge of an area of infarction, left ventricular infarct sites, normal right ventricular sites, and endocardial catheter sites. The Bonferroni method was used to adjust the level of each test so that the overall error rate was no greater than 0.05. A chi-square test was also used to compare the degree of success for left vs right ventricular endocardial catheter sites. A t test was used to compare the excitability thresholds of sites within normal vs sites within infarcted myocardium.

**Results**

The initiation of sustained ventricular tachyarrhythmias was attempted at 232 sites in these 24 dogs (mean 10 ± 5 (SD) sites/animal), and five to 24 sites were evaluated in individual dogs. Strength-interval curves were constructed at each of these sites and correlated with the ability to initiate sustained ventricular tachyarrhythmias. Figures 1–3 illustrate the results of electrophysiologic studies done in one dog 15 days after infarction. Programmed electrical stimulation initiated sustained ventricular tachyarrhythmias reproducibly at four of 13 (31%) of the sites attempted in this animal (fig. 1), including sites within the distribution of both occluded and nonoccluded vessels. Figure 2 illustrates the initiation of sustained ventricular tachycardia from site 1, which was located 1.0–1.5 cm from the edge of the area of infarction in the distribution of a nonoccluded diagonal vessel. Sustained ventricular tachycardia with a cycle length of 120–140 msec was initiated reproducibly from this site using double ventricular extrastimuli, introduced during ventricular pacing at cycle length 300 msec.

The results were much different with programmed stimulation from left ventricular site 2 (fig. 1), a normal site more than 4 cm from the edge of the area of infarction. Although we captured the ventricle at es-

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**Figure 1.** Diagram of the heart showing the relative locations of the 13 sites from which programmed electrical stimulation was done in an experimental animal studied 15 days after infarction. The left ventricular anterior free wall (LV), the right ventricle (RV) and the left ventricular apex are indicated. The lightly stippled area represents the extent of mottled infarction. The circled numbers represent sites from which sustained ventricular tachyarrhythmias could be initiated, and numbers not circled represent sites from which sustained ventricular tachyarrhythmias could not be initiated using programmed pacing with twice-diastolic-threshold current.
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FIGURE 2. Analog records obtained during pacing at left ventricular site 1 (see figure 1). The schematic on the right indicates the location of site 1 in normal myocardium, in close proximity to the area of infarction (stippling). Records include surface ECG leads 2 and V10 and recordings from multiple left ventricular bipolar plunge electrode sites labeled R1 through R7. The stimulus artifact (S) plus time lines (time) are also represented. During ventricular pacing at a cycle length (CL) of 300 msec, two ventricular extrastimuli (VES) were introduced at coupling intervals of 140 and 240 msec and sustained ventricular tachycardia (VT) with a cycle length of 120-140 msec could be initiated reproducibly. RV = right ventricle; LV = left ventricle.

FIGURE 3. Strength-interval curves derived from measurements made at the four left ventricular (LV) sites illustrated in figure 1. Coupling intervals (msec) are plotted vs the maximum milliamperage failing to elicit a response at that coupling interval. Measurements of excitability thresholds, effective refractory periods, relative refractory periods, and ventricular refractory periods (VRP) at twice-diastolic threshold for these four sites are detailed in table 1.
sentially the same coupling intervals that were successful in initiating sustained ventricular tachycardia when introduced at left ventricular site 1, neither sustained ventricular tachycardia nor more than two repetitive ventricular responses was initiated using double ventricular extrastimuli from this site. Ventricular tachycardia could not be initiated from left ventricular site 2 at these or any other coupling intervals. Three ventricular extrastimuli, however, did result in nonsustained three- to six-beat salvos of repetitive ventricular responses.

Programmed pacing from left ventricular site 3, located just within the area of infarction and less than 2 cm from left ventricular site 1 (fig. 1), was also unsuccessful. At this abnormal site, the ventricular refractory period using stimuli of twice-threshold intensity was relatively prolonged (188 msec), and we could not capture the ventricles with double ventricular extrastimuli at coupling intervals less than 190 and 340 msec (S1S2, S1S3, respectively). No repetitive ventricular responses and no ventricular tachycardia resulted from programmed pacing at this site with double or triple ventricular extrastimuli.

Programmed stimulation at left ventricular site 4, another site within the area of infarction and only 2–3 mm from site 3, was also unsuccessful. At this site, we captured the ventricle at coupling intervals (160 and 280 msec) comparable to those that were successful in initiating ventricular tachycardia when introduced from left ventricular site 1. At these relatively short coupling intervals, four- to 10-beat runs of nonsustained ventricular tachycardia were reproducibly initiated. However, we could not initiate sustained ventricular tachycardia from this site even with repeated attempts using multiple combinations of coupling intervals and multiple cycle lengths. Pacing from sites 3 and 4 (not shown), although only 2–3 mm apart, resulted in the morphology of the paced QRS complexes being markedly different. However, pacing from sites 1 and 3, although > 15 mm apart, resulted in almost identical paced QRS complexes.

Only one left ventricular site from within the area of infarction, of the four attempted in this dog, was successful in initiating sustained ventricular tachycardia. This site (fig. 1) was located near the apical edge of the infarct, approximately 1.5 cm from left ventricular site 4 and 3 cm from left ventricular site 1. At this site, ventricular tachycardia was initiated with double ventricular extrastimuli at coupling intervals of 150 and 270 msec and with a morphology similar to the ventricular tachycardia initiated from site 1.

In every dog in which we initiated at least four repetitive beats of nonsustained ventricular tachycardia from any site, we could also initiate sustained ventricular tachyarrhythmias from at least one site when enough sites were evaluated.

Figure 3 displays strength-interval curves constructed from electrophysiologic measurements made at left ventricular sites 1–4 (fig. 1). Left ventricular sites 1 and 2, which were in the distribution of nonoccluded vessels, had typically normal strength-interval curves. Curves were smooth, without inflections, and had rapid transitions from relative refractory periods to ERPs. Sites 3 and 4 were within the area of infarction and each had an abnormal strength-interval curve. At these sites, excitability thresholds were increased, and the ERPs, RRs, and VRPs (measured at twice-diastolic-excitability threshold) were all prolonged (table 1). In addition, left ventricular sites 3 and 4 were also markedly different from each other in measurements of excitability and refractoriness, although only a few millimeters apart anatomically. Thus, site 3, which had markedly abnormal properties of excitability and refractoriness, was not a suitable site for the initiation of ventricular tachycardia; at site 4, which had only mildly abnormal electrophysiologic properties, we initiated salvos of nonsustained repetitive responses. At site 6 (strength-interval curve not shown), where measurements of excitability and refractoriness were essentially normal, sustained ventricular tachycardia was initiated reproducibly.

Table 1. Excitability, Refractory Period Measurements at the Four Left Ventricular Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>ET (mA)</th>
<th>ERP (msec)</th>
<th>RRP (msec)</th>
<th>VRP (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.10</td>
<td>127</td>
<td>134</td>
<td>134 (at 0.20 mA)</td>
</tr>
<tr>
<td>2</td>
<td>0.03</td>
<td>122</td>
<td>137</td>
<td>139 (at 0.06 mA)</td>
</tr>
<tr>
<td>3</td>
<td>1.76</td>
<td>178</td>
<td>238</td>
<td>194 (at 3.52 mA)</td>
</tr>
<tr>
<td>4</td>
<td>0.34</td>
<td>140</td>
<td>170</td>
<td>160 (at 0.68 mA)</td>
</tr>
</tbody>
</table>

Abbreviations: ERP = effective refractory period; ET = excitability threshold (mA); LV = left ventricular; RRP = relative refractory period; VRP = ventricular refractory period at twice-diastolic-excitability threshold.

Figure 4 illustrates the strength-interval curve from one infarct site in another dog studied 4 days after ligation followed by reperfusion of the mid-left anterior descending coronary artery. No arrhythmias were inducible from this infarct site with single or double ventricular extrastimuli of twice-threshold intensity, although double ventricular extrastimuli from a normal site located < 2 cm away had been successful using twice-threshold current. The VRP at twice threshold was 182 msec at this infarct site and double ventricular extrastimuli failed to capture at intervals shorter than 184 and 330 msec. At this same time, using twice-threshold drive pacing and extrastimuli of five times threshold (0.60 mA), again at coupling intervals of 184 and 330 msec, no arrhythmias were initiated. However, as revealed by the strength-interval curve, using stimuli of 0.60-mA intensity, we could then capture the ventricle at much shorter coupling intervals. At coupling intervals of 172 and 304 msec, we could initiate sustained ventricular tachyarrhythmias from this infarct site. This indicates that local excitability and refractoriness at this site, rather than the location of the site per se, were the critical factors limiting arrhythmia initiation. Similarly, in other dogs, five-times-diastolic-threshold extrastimuli never initiated a sustained tachyarrhythmia at coupling intervals that had failed with twice-threshold stimuli. Rather, it was the ability to "walk in" on the strength-
interval curve and capture at critical, shorter coupling intervals using higher threshold stimuli that appeared to facilitate arrhythmia initiation. Arrhythmias were never initiated using five-times-threshold ventricular extrastimuli in any case in which we could not also initiate ventricular tachyarrhythmias in the same dog at some other site using twice-threshold stimuli.

In seven of the 24 dogs with inducible sustained ventricular tachyarrhythmias, we initiated sustained arrhythmias using just one extrastimulus of twice-threshold intensity from at least one site. However, of the total of 72 sites evaluated in these seven dogs, 36 sites (50%) failed to initiate sustained arrhythmias, even with three ventricular extrastimuli of twice-threshold intensity.

Overall, for the 24 dogs studied using twice-threshold stimuli, sustained ventricular tachyarrhythmias were most easily initiated from normal left ventricular plunge electrode sites within 2 cm of areas of infarction (27 of 44, 61%). Less successful sites included normal left ventricular plunge electrode sites at a greater distance from the edge of the area of infarction (eight of 32, 25%) \((p = 0.002)\), plunge electrode sites within an area of infarction (20 of 103, 19%) \((p < 0.001)\), normal right ventricular plunge electrode sites (five of 24, 21%) \((p < 0.001)\), and endocardial catheter sites selected on the basis of normal diastolic excitability thresholds (six of 29, 21%) \((p < 0.001)\); these other sites were all comparable \((p > 0.05)\) in their relative rate of success in initiating ventricular tachyarrhythmias. Although relatively few sites were studied, there was also no difference \((p > 0.05)\) in the degree of success of right (one of 10, 10%) vs left (five of 19, 26%) \((p > 0.05)\) ventricular endocardial catheter sites.

The proportion of successful sites using twice-threshold stimuli ranged from eight of 10 (80%) to one of 17 (6%). As noted in the Methods section, three sham-operated control animals were also studied. In each case, at least 15 sites were attempted, using three ventricular extrastimuli at each site, and in addition, short bursts (2–5 seconds) of rapid ventricular pacing (cycle length 120–150 msec) were also applied. No episodes of either four or more beats of nonsustained ventricular tachycardia or sustained ventricular tachycardia were initiated with these methods in the three sham dogs. Two more dogs were studied and also excluded from statistical analysis. Each had undergone ligation and reperfusion of the mid-left anterior descending coronary artery. Neither dog had inducible arrhythmias from the 15 sites studied in each. All sites studied also had normal strength-interval curves. At postmortem examination, each of these two dogs had a large anastomosing circumflex coronary artery system and multiple small punctate \((\leq 1 \text{ mm}^2)\) areas of infarct \((\text{total} < 0.5 \text{ cm} \times 0.5 \text{ cm})\) were distributed over 2 cm × 3 cm. By chance, none of the plunge electrodes had situated in one of these punctate areas of necrosis, explaining the normal strength-interval curves.
Histopathologic Findings

Postmortem examination of the hearts of the study dogs revealed mottled infarctions with close interspersing of normal and abnormal myocardium as previously described in this model of chronic myocardial infarction.\(^{21}\) All sites with normal excitability and refractoriness from within the distribution of non-occluded vessels were confirmed to be normal in each case. None of the three sham-operated controls had any area of infarction evident 4 days after their initial procedure; postmortem examination revealed only minor epicardial damage at the site of coronary artery dissections.

Discussion

The present study has demonstrated the potential importance of the site of stimulation to the initiation of sustained ventricular tachyarrhythmias in a canine model of chronic myocardial infarction. The results suggest that both local electrophysiologic properties of excitability and refractoriness, as well as the location of a site with respect to the potential areas of arrhythmogenesis, may be critical.

Basic and clinical investigators have also considered the importance of the site of stimulation to both the initiation and termination of sustained tachyarrhythmias using programmed pacing techniques.\(^4,\ 6,\ 8,\ 10\) Examples include the elegant experiments of Allessie and co-workers in isolated rabbit right atrial tissue preparations.\(^2,\ 20\) In their in vitro studies, the arrhythmias initiated by programmed pacing had characteristics suggesting a reentrant mechanism.\(^8,\ 27\) Clinically, the importance of the site of stimulation to the initiation of reentrant tachycardias has been best defined in patients with preexcitation syndromes (e.g., Wolff-Parkinson-White).\(^8,\ 28,\ 29\) In addition, theoretical and applied work has been done to better define the various electrophysiological properties of myocardium that may also be related to the technique of programmed stimulation.\(^30-38\)

Although it has been assumed that a complex interaction of anatomic (e.g., normal, infarct), geometric (e.g., topography, fiber orientation) and electrophysiologic factors may be critical to the initiation of ventricular tachyarrhythmias in man,\(^8\) systematic experimental studies are needed. However, inconsistencies reported by different clinical electrophysiologic laboratories in their ability to initiate sustained ventricular tachyarrhythmias, or in their interpretation of serial antiarrhythmic drug studies, may be explained in part by factors related to the site of stimulation.\(^8,\ 12,\ 13,\ 16,\ 18\)

The present canine model of chronic myocardial infarction is well-suited to a systematic analysis of the importance of the site of stimulation in initiating arrhythmias. Using methods of programmed electrical stimulation comparable to those used in the clinical laboratory, ventricular tachyarrhythmias can be initiated with characteristics similar to those of man.\(^31\) The arrhythmias initiated using these methods have characteristics most consistent with a microreentrant mechanism.\(^8-10,\ 21,\ 27\) although other pathophysiologic mechanisms cannot be excluded.\(^17,\ 39-43\) The present study has clearly demonstrated that the site of stimulation can be critical to the initiation of sustained ventricular tachyarrhythmias. In this canine infarction model, differences of 1–2 mm in distance were critical within areas of infarction; within otherwise normal areas, distances of 1–2 cm were often critical to arrhythmia initiation even in the relatively small heart of an 8–16-kg dog (figs. 1 and 2).

One cannot always determine in the clinical catheterization laboratory whether sites are normal. Using catheter techniques, diastolic excitability thresholds tend to be higher (e.g., \(\geq 0.30\) mA) even for normal myocardium compared to the excitability thresholds obtained in canine studies (e.g., 0.02–0.24 mA) using plunge electrodes of small diameter and surface area.\(^21,\ 36,\ 44,\ 46\) The present study points out that even sites with relatively normal diastolic excitability thresholds may have markedly abnormal refractory period measurements. Furthermore, in the catheterization laboratory, the limits of resolution are probably \(\geq 2\) cm; whereas using plunge electrodes, 1–2-mm distances can be resolved.

As determined by the construction of strength-interval curves in the present study (figs. 3 and 4), sites with normal excitability and refractoriness located less than \(2\) cm from the edge of an area of infarction, and presumably in proximity to the area of the microreentrant circuit, were most often successful in the initiation of sustained ventricular tachyarrhythmias. Using stimulation techniques, we cannot, of course, comment on the importance of the site of origin of spontaneous premature beats. Similarly, the present analysis provides no information regarding either the characteristics of the conduction pathway from the site of origin of the extrastimulus to the presumed microreentrant circuit, or the local properties of excitability and refractoriness at the site of entry into the arrhythmia circuit.

Additional cautions must be exercised before extrapolating from the results of these studies to those performed in man. For example, in this chronic canine model, the infarcts are mottled with close interspersing of normal and abnormal myocardium throughout.\(^51\) In human infarctions, in which such heterogeneity is often confined to broad border areas, the actual site of stimulation may not be as critical on a millimeter-to-millimeter basis. Also, with plunge electrodes, intramyocardial activation patterns may be more complex than those that result from endocardial catheter stimulation techniques, in which the specialized Purkinje conduction system may be engaged more directly.

Furthermore, in the present model, infarctions are small by design and often limited to the distal anterior apical free wall. Clinically, most patients studied with sustained ventricular tachyarrhythmias have large healed areas of myocardial infarction, so that either the right ventricular apex or right ventricular outflow tract is usually in close proximity to these areas of
damage and potential reentrant circuits. Also, these right ventricular endocardial catheter sites are usually in areas free of infarction and have normal excitability and refractoriness. In our experimental model, normal right ventricular sites are usually not in close proximity to areas of infarction. These differences help to explain the greater degree of success reported in man using right ventricular pacing sites than in our canine model.6,13 Moreover, in man, additional anatomic barriers, such as mural thrombi, aneurysms, fibrosis and scars from previous myocardial infarctions, may further limit access to potential reentrant circuits using endocardial catheter techniques.

Thus, in performing clinical ventricular tachyarrhythmia studies, our results suggest it would be more advantageous to pace from normal sites near areas of suspected reentrant circuits. If pacing from these sites at twice-diastolic threshold fails, then stimuli of five-times-diastolic-threshold intensity might be attempted. Similarly, in patients in whom sustained ventricular tachyarrhythmias have been documented clinically, or in those in whom it is strongly suspected, multiple pacing sites should be tried.

Furthermore, in performing serial drug studies, if one is to suggest that an arrhythmia is no longer inducible after a particular intervention, the same site must be studied after the intervention that was successful in arrhythmia initiation before the intervention. Fluoroscopy may not always provide enough resolution for this purpose. Comparing activation sequences during pacing, however, may provide some information concerning the reproducibility of the site of stimulation.44 In addition, when a drug appears to prevent the initiation of arrhythmias, it still seems advisable to consider further attempts at arrhythmia initiation from other sites using both twice- and five-times-threshold-intensity stimuli.

Our studies provide further understanding of the electrophysiologic and anatomic factors that may play a role in the more optimal application of programmed pacing to the evaluation and design of successful therapy for potentially lethal ventricular tachyarrhythmias.

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