Strength-Interval Relations in a Chronic Canine Model of Myocardial Infarction

Implications for the Interpretation of Electrophysiologic Studies

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SUMMARY  Fifteen adult mongrel dogs underwent two-stage occlusion of the mid- or distal left anterior descending coronary artery and then a reperfusion stage. The dogs were studied 3–30 days later to determine strength-interval relations in a canine model of chronic myocardial infarction. These dogs were susceptible to the initiation of sustained ventricular tachyarrhythmias with the introduction of one, two or three ventricular extrastimuli. Using unipolar cathodal stimuli with a pulse width of 2 m sec, strength-interval curves were constructed from measurements made at multiple sites in the distribution of occluded and nonoccluded vessels during drive pacing at a cycle length of 300 m sec. At 56 normal sites, ventricular refractory periods measured at twice-diastolic-excitability threshold approximated the relative refractory periods (mean absolute difference 3 m sec), but were variably longer than effective refractory periods (mean difference 18 m sec, range 4–29 m sec). At 51 infarct sites, differences between ventricular refractory periods measured at twice-diastolic-excitability threshold and both relative refractory periods (mean difference 13 m sec, range –60 to +18 m sec) and effective refractory periods (mean difference 28 m sec, range 1–60 m sec) were markedly disparate. These differences were further exaggerated after administration of i.v. procainamide. These findings suggest limitations in interpreting the results of programmed pacing studies performed using stimuli of twice-threshold intensity.

PROGRAMMED ELECTRICAL STIMULATION has gained acceptance clinically as a means of initiating and terminating sustained tachyarrhythmias,1–8 studying arrhythmia mechanisms,7–9,12 evaluating properties of excitability and refactoriness,5–15 and determining the electrophysiologic effects of various pharmacologic and antiarrhythmic interventions.4,6,7,13,18–22

In clinical practice, bipolar pacing via a multipolar catheter is initiated at a rate faster than the patient’s intrinsic rate, and the milliamperage of a 1–2-msec pulse is increased until consistent capture is evident. The minimum milliamperage necessary for capture is then defined as the excitability threshold for that site.23 Routinely, clinical electrophysiologic studies have been performed at a milliamperage approximately twice the excitability threshold, and usually at less than 3 mA.4,7,8,24 Such methods have been considered adequate for obtaining necessary electrophysiologic information and safe enough to avoid inadvertent ventricular fibrillation.7,8,24 However, no specific data suggest that performing programmed electrical stimulation at twice-diastolic-threshold intensity is optimal. Even in the most experienced clinical laboratories, success with this technique has not been complete.4,7,8,24,26 Also, some investigators have reported variable results in attempts to initiate sustained ventricular tachyarrhythmias, even in the same patient, during serial studies on successive days.27

Recently, canine models of chronic myocardial infarction were developed in which dogs are susceptible to the reproducible initiation of sustained ventricular tachyarrhythmias using methods of programmed electrical stimulation comparable to those used in the clinical laboratory.28–30 These models appear well-suited to the critical evaluation of electrophysiologic techniques used routinely in clinical practice. The present studies were designed specifically to evaluate strength-interval relations and to determine the implications of these relations to the interpretation of electrophysiologic data obtained during programmed pacing. Strength-interval curves were constructed from electrophysiologic measurements made at multiple ventricular sites in areas of normal and abnormal myocardium in an experimental canine model of myocardial infarction susceptible to arrhythmia initiation.30

Materials and Methods

Studies were performed on 15 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 pharyngeotracheal 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 was opened and a pericardial sling was created. The 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 the dogs were pretreated with a bolus of 2 mg/kg lidocaine intravenously and 5 minutes after release with a second lidocaine bolus (1 mg/kg). No episodes of ventricular fibrillation were 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 occlusions, when the dogs were otherwise clinically stable and the accelerated ventricular arrhythmias of the first 24–48 hours had subsided, they were anesthetized with i.v. sodium pentobarbital (10–20 mg/kg) plus diazepam (1–2 mg/kg) or i.v. sodium 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 plunge (hook) wire electrodes (0.1 mm diameter) were placed in multiple subepicardial, intramyocardial and subendocardial sites within areas of both occluded and non-occluded 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 spreader 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.).

The dogs were evaluated initially to confirm their susceptibility to sustained ventricular tachyarrhythmias. Using unipolar cathodal stimuli 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 dogs had sustained ventricular tachyarrhythmias inducible reproducibly either one (n = 6 dogs), two (n = 5 dogs) or three (n = 4 dogs) ventricular extrastimuli of twice-threshold intensity. Sustained ventricular tachyarrhythmias were defined as non-self-terminating (> 1 minute) ventricular tachycardia (cycle length ≥ 120 msec; six dogs), ventricular flutter (cycle length 100–120 msec, regular rhythm; four dogs) or ventricular fibrillation (five dogs). Three sham-operated controls and two study dogs did not have inducible arrhythmias with either programmed pacing or short bursts of rapid ventricular pacing (cycle length 120–150 msec) and were not included in this analysis. Each of the two study dogs with no inducible arrhythmias had a large anastomosing circumflex coronary artery system and less than 0.5 cm × 0.5 cm of infarct dispersed over an area of at least 2 cm × 3 cm, apparent postmortem.

Measurements of Excitability and Refractoriness

Using unipolar cathodal stimulation, thresholds for excitability were determined at each electrode site. 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 (V₂) after eight ventricular drive beats at a basic cycle length of 300 msec. In dogs with less than 1:1 retrograde ventriculoatrial 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 V₂. When S₂ failed to elicit a V₂, the milliamperage of S₂ was then increased incrementally until a V₂ was elicited, and the coupling interval decreased until S₂ again failed to elicit a V₂. This sequence was repeated until an effective refractory period was reached at a maximum of 10 mA. The effective refractory period, therefore, was defined at the longest S₁S₂ interval that failed to elicit a V₂ 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 current intensity. This was done by first setting the coupling interval for S₂ and then increasing the current from 0 to the minimum current required for eliciting a V₂ 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 unipolar anodal and bipolar stimulation. A drive pacing rate of 300 msec was chosen to facilitate consistent capture in all dogs.

The relative refractory period was defined as the longest coupling interval along the strength-interval curve at which the current required to evoke a response (V₂) increased above the diastolic excitability threshold by greater than 0.025 mA for a 1-msec change in the coupling interval. This criterion was chosen to provide adequate resolution and consistency in determining the longest coupling interval which showed an increased threshold current requirement for stimulation. For this study, the ventricular refractory period at each site 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. This definition was chosen to conform with conventional clinical practice, in which programmed stimulation is routinely done using twice-threshold current. Properties of threshold for excitability (i.e.,
minimum current eliciting a V₂ at a long diastolic coupling interval), effective refractory period, relative refractory period, and ventricular refractory period at twice-diastolic-excitability threshold were determined for multiple subendocardial, intramyocardial and subepicardial sites from within the distribution of occluded and nonoccluded vessels in each dog. The limit of resolution for refractory period measurements was within ± 1 msec. Electrophysiologic properties at multiple sites were reevaluated throughout the study, both before and after all interventions (including countershock) to validate the stability of measurements at different sites over time. Refractory period measurements remained stable to within ± 1 msec and excitability thresholds to within ± 0.02 mA over the course of each experiment. In selected experiments, strength-interval curves were also constructed before and 20-30 minutes after infusion of 10-30 mg/kg procainamide, when plasma procainamide concentrations ranged from 8.2-19.5 μg/ml.

Postmortem Examination

After electrophysiologic studies were completed, dogs were sacrificed with plunge electrodes in situ, and each plunge electrode position was confirmed at postmortem examination using 1-2-mm-thick slices of myocardium. Hearts were then thin-sectioned and histopathologic studies done using either hematoxylin-eosin, trichrome or nitroblue tetrozole 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.

Statistics

Electrophysiologic data were analyzed using the t test. Pooled data were analyzed using a comparison of means to compare differences between ventricular refractoriness at twice threshold and measurements of effective and relative refractory periods for normal vs infarct sites. Comparisons of paired samples were used to analyze the differences in measurements of excitability thresholds, effective refractory periods, relative refractory periods and ventricular refractory periods made at sites within the distribution of occluded and nonoccluded vessels.

Results

Strength-interval curves were constructed from electrophysiologic measurements made at 56 normal and 51 infarct sites in 15 dogs with inducible sustained ventricular tachyarrhythmias. Figure 1 shows strength-interval curves derived from measurements made at three intramyocardial sites in close proximity in a dog studied 17 days after experimental infarction. Site 1 was located at the edge of the area of infarction in the distribution of a nonoccluded diagonal vessel, and sites 2 and 3 were just within the area of infarction, only 2-3 mm from each other and less than 2 cm from site 1. Measurements at site 1 resulted in a typical normal strength-interval curve with a low excitability threshold (0.06 mA) and short effective refractory period (138 msec) during drive pacing at a cycle length of 300 msec. The curve was smooth without inflections and made a rapid transition from the relative to the effective refractory period. As was characteristic of most normal sites, the ventricular refractory period was 160 msec, almost equal to the relative refractory period of 154 msec but moderately longer than the effective refractory period of 138 msec.

Table 1 summarizes the measurements made at 56 normal sites. At normal sites, mean values for the ventricular refractory period were approximately equal to those for the relative refractory period at the normal sites, with a mean absolute difference of 3 msec. The absolute differences between ventricular and relative refractory periods are detailed because measurements of refractoriness at twice-diastolic-excitability threshold were variably longer or shorter than relative refractory periods at individual sites. The differences between ventricular and relative refractory periods ranged from −10 to 12 msec at these same sites. The ventricular refractory periods measured at twice threshold were an average of 18 msec greater than the effective refractory periods for these same sites. The
differences between refractoriness at twice threshold and the effective refractory periods ranged from as little as 4 msec to as much as 29 msec, even at the relatively short pacing cycle length of 300 msec.

In addition to a normal strength-interval curve (site 1), figure 1 also displays two abnormal strength-interval curves derived from measurements made at left ventricular sites 2 and 3. Although site 2 was located within the area of infarction, the excitability threshold at this site was normal, 0.10 mA. However, both the effective and relative refractory periods at site 2 were moderately prolonged, to 172 and 202 msec, respectively. The ventricular refractory period at this site was 210 msec. Left ventricular site 3 was only 2–3 mm from site 2 within the area of infarction. At this site, the excitability threshold was increased to 1.80 mA, the strength-interval curve was splayed and had abnormal inflections. The effective and relative refractory periods were markedly prolonged, to 194 and 260 msec, respectively. Although the ventricular refractory period was again 210 msec, the same as it was at normal left ventricular site 2, all other measurements, including the excitability threshold, effective refractory period and relative refractory period, were markedly different from those at site 2. Furthermore, at site 3, the ventricular refractory period was considerably shorter (by 50 msec) than the relative refractory period.

Table 1 also summarizes measurements of excitability and refractoriness made at 51 infarct sites in these 15 dogs. There were marked and variable differences between refractoriness at twice diastolic threshold and both effective and relative refractory periods. This variability is reflected in the wide ranges of values and large standard deviations. Even at the relatively short cycle length of 300 msec, the mean difference between the ventricular and effective refractory periods for these 51 infarct sites was 28 msec. The differences for these measurements ranged from a minimum of 1 msec to as much as 60 msec. The mean absolute difference between ventricular refractory periods and relative refractory periods at these 51 sites was 13 msec. Similarly, differences between the ventricular and relative refractory periods ranged from –60 to +18 msec. Thus, at abnormal sites, there was no consistent relationship between measurements of ventricular refractoriness at twice threshold and measurements of either effective or relative refractoriness. Measurements of refractoriness at twice-diastolic-excitability threshold usually fell along portions of strength-interval curves where small changes in milliamperage resulted in marked and variable changes in refractoriness (fig. 1). This portion of the curve was often splayed and prolonged at abnormal sites, further exaggerating these disparities. Although measurements of refractory periods within areas of infarction had a wide range of values, differences between normal and infarct areas were highly significant (p < 0.001) (table 1).

In selected dogs, additional studies were done to further define limitations of twice-threshold refractoriness in the initiation of ventricular arrhythmias. Figure 2 displays two strength-interval curves derived from a dog studied 8 days after experimental infarction. One ventricular extrastimulus (at coupling intervals ≤ 160 msec) introduced from site 1, a normal left ventricular site at the edge of the area of infarction, reproducibly initiated sustained ventricular tachycardia. However, at site 2, only 2 cm away, but within the area of infarction, no ventricular tachycardia was inducible. The refractory period at twice threshold at this abnormal site was prolonged to 200 msec. Programmed pacing was then done at site 2, still at a coupling interval of 200 msec and using drive pacing at twice-threshold intensity, but with extrastimuli of five-times-threshold intensity (0.60 mA). Again, no ventricular tachycardia resulted. The coupling interval of the extrastimulus was then shortened in 2-msec steps. Using an extrastimulus of five-times-threshold intensity rather than twice threshold, we could capture the ventricle at coupling intervals as short as 146 msec; at coupling intervals as close as 164 to 146 msec we could initiate sustained ventricular tachycardia reproducibly from this site.

Figure 3 illustrates strength-interval curves constructed from measurements made at one site in another dog 4 days after infarction. Measurements were made at this site, within the area of infarction,
before and 20 minutes after i.v. administration of 20 mg/kg procainamide. At this site, ventricular tachycardia was reproducibly initiated at coupling intervals of < 160 msec before procainamide using stimuli of twice-diastolic-threshold intensity. After procainamide, again using stimuli of twice-threshold intensity, ventricular tachycardia was no longer inducible. However, after procainamide, the shortest coupling interval permitting ventricular capture using twice-threshold stimuli was prolonged to 194 msec. The intensity of the extrastimulus was then increased to five times the excitability threshold (5.0 mA). At this same long coupling interval (194 msec), using twice-threshold-drive pacing and five-times-threshold extra-stimuli, no repetitive ventricular responses resulted. However, using this increased extrastimulus intensity, we could capture the ventricle at much shorter coupling intervals. At a coupling interval of 180 msec, ventricular tachycardia was again initiated, although the cycle length of the ventricular tachycardia was increased to 250 msec, compared with 130 msec before procainamide administration. Twenty minutes after administration, at a time when the plasma procainamide concentration was 16.3 μg/ml, the procainamide had only minimal effect on the excitability threshold and moderate effect on the effective refractory period at this site. However, the ventricular refractory period was markedly prolonged at this site, to 192 msec, compared with 150 msec before procainamide. Thus, although initial results using twice-threshold extrastimuli suggested a completely salutary effect of procainamide in terms of preventing the initiation of sustained ventricular tachycardia, pacing with stimuli of higher intensity revealed that this response was not completely satisfactory. In each dog in which a sustained ventricular tachycardia was initiated using extrastimuli of five-times-threshold intensity, we could also initiate the same tachyarrhythmia from at least one other site using twice-threshold stimuli. There was no evidence that the use of five-times-threshold current was in and of itself arrhythmogenic.

**Histopathologic Findings**

All 15 dogs had small (≤ 3 × 3 cm) (usually less than 2 × 3 cm) mottled infarctions with close interspersing of normal and abnormal myocardium throughout subendocardial, intramyocardial and subepicardial layers. Areas of normal myocardium often survived even within areas of the most dense infarction and necrosis. Infarctions involved the anterior apical left ventricular free wall, often sparing the interventricular septum. Sites within the distribution of nonoccluded vessels and with normal excitability and refractoriness were confirmed to be normal on postmortem examination. Histopathologic findings in this model of chronic myocardial infarction have been described.30
Discussion

The present study was designed to evaluate the implications of strength-interval relations to the interpretation of electrophysiologic data obtained during programmed pacing. We examined possible limitations in interpreting electrophysiologic data obtained using stimuli of twice-diastolic-threshold intensity. The use of twice-threshold current is routine practice in most clinical laboratories.4-8,24 For this study, we constructed strength-interval curves at multiple sites in the distribution of occluded and nonoccluded vessels in a model of chronic myocardial infarction susceptible to the initiation of sustained ventricular tachyarrhythmias.

The strength-interval curves (figs. 1 and 2) reveal that sites with similar excitability threshold can have markedly disparate ventricular refractory periods, including those measured at twice threshold. Thus, determining the excitability threshold, which is the usual variable used clinically to determine that a site is acceptable for pacing or programmed electrical stimulation, is not sufficient to identify those sites which have normal refractoriness. Moreover, sites only millimeters apart may have widely disparate properties of excitability and refractoriness (fig. 1). These findings suggest potential difficulties in evaluating refractoriness during serial studies done at different times, or in studies done before and after various interventions.

Ventricular refractoriness measured at normal sites using twice-diastolic-threshold stimuli permitted approximation of the relative refractory period but did not permit approximation of the effective refractory period (table 1). At abnormal sites, however, measurements of ventricular refractory periods varied markedly with respect to both effective and relative refractory periods (table 1). Even at the relatively short paced cycle length of 300 msec, differences between refractoriness measured at twice threshold and effective or relative refractory periods varied by as much as 60 msec. More marked disparity might be anticipated in clinical studies in which cycle lengths ranging from 800-400 msec are often used for drive pacing.5-8,10,12,15,18

Basic properties of excitability and refractoriness have also been studied as a means of better defining arrhythmia and antiarrhythmic mechanisms.35-47 However, most clinical data have been limited to studies using measurements of refractoriness obtained with stimuli of only one intensity, and this intensity has been twice diastolic threshold. The findings in the present study demonstrate possible problems in interpreting data obtained using stimuli of only one intensity (figs. 1-3). To relate either arrhythmic or antiarrhythmic mechanisms to properties of excitability and refractoriness, it may be necessary to obtain more detailed information, such as that available from constructing strength-interval curves.30,42,45

The present studies also provide insight into the clinical difficulties in the initiation of sustained ventricular tachyarrhythmias in patients with clinically documented tachycardia episodes.4,7,8,27 In some clinical cases, the mechanisms of the arrhythmias may be such that the routine methods of programmed electrical stimulation are not suitable for arrhythmia initiation.48,49 However, even in hearts susceptible to arrhythmia initiation, the ventricular refractory period using twice-threshold-intensity current may be so prolonged at an abnormal site, even at a site with normal threshold excitability, that it may never be possible to capture the ventricle from that site at coupling intervals short enough to initiate an arrhythmia (figs. 1 and 2).

The use of current of increased intensity was never sufficient in and of itself to initiate sustained ventricular tachyarrhythmias; rather, it merely facilitated shortening of the coupling interval by "walking in" (figs. 2 and 3) on the strength-interval curve. Thus, it was the ability to introduce stimuli at shorter coupling intervals that apparently allowed arrhythmia initiation. Therefore, the present studies suggest that sites with normal excitability thresholds should be used preferentially for stimulation studies.7,50 If necessary, multiple normal sites should be attempted. If these steps fail, programmed pacing should be done using a current intensity increased from twice to three to five times threshold. However, the applicability of these findings to clinical studies in man must be verified prospectively.

The present studies suggest further limitations in the evaluation of antiarrhythmic drugs in the treatment of sustained ventricular tachyarrhythmias. Agents such as procainamide may markedly affect the strength-interval curve, especially at sites within abnormal myocardium (fig. 3).10,21,47,51 Although excitability thresholds and effective refractory periods may be only minimally affected, measurements of refractoriness at twice-diastolic-excitability threshold may be markedly and disproportionately prolonged. Therefore, after administration of procainamide, it may be difficult to introduce twice-threshold stimuli at coupling intervals short enough to initiate sustained ventricular tachyarrhythmias. Thus, one should be cautious in ascribing a beneficial antiarrhythmic effect to any intervention merely because an arrhythmia was no longer initiated using a stimulus of a given intensity, arbitrarily chosen as twice threshold. This limitation of twice-threshold stimuli may help to explain some of the inconsistencies reported in arrhythmia initiation and treatment.4,7,8,26,27

Our findings in this study also highlight the potential hazards of pacing the ventricle with greater than twice-threshold stimuli either in the angiographic catheterization laboratory, in the postoperative open-heart patient, or with permanently implanted units, especially during fixed-rate pacing. Use of increased current may facilitate ventricular capture at coupling intervals short enough to initiate arrhythmias in susceptible patients. Earlier reports of high-current-output pacemaker-induced arrhythmias undoubtedly included patients in whom this phenomenon occurred.52-65

Thus, the present studies confirm the importance of
programmed stimulation to the study of arrhythmias, but they also suggest that further modifications of this technique may lead to its more optimal use in defining arrhythmia mechanisms, revealing the mechanisms of antiarrhythmic drugs, and in the management of patients with tachyarrhythmias. Such modifications must be evaluated prospectively.

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