ABSTRACT
The relationship of the form of ventricular anodal strength-interval curves to the types of arrhythmias induced by trains of low-intensity stimuli was studied in 16 dogs. Strength-interval curves were determined after basic atrial driven beats and after induced premature ventricular depolarizations. The test stimuli for these determinations were 2-msec anodal square waves delivered in 1-msec decrements during the first half of the cardiac cycle and in 10-msec decrements during the last half of the cycle. At each time step, the stimulus intensity was increased in 5-μamp steps until a ventricular response occurred or a level of 1.2 mamp was reached. Three types of strength-interval curves were observed. Each form of the strength-interval curve was associated with a specific type of arrhythmia induced by a train of 50-Hz, 2-msec anodal stimuli of minimum threshold intensity which was applied for periods of up to several minutes. When the minimum threshold in the strength-interval curve following the basic driven beat was lower than the minimum threshold following the induced premature ventricular depolarization, the train of stimuli induced stable ventricular bigeminy. Accelerating ventricular tachycardia followed by ventricular fibrillation resulted if there were deep dips in the strength-interval curves following both the basic driven beats and the premature ventricular depolarizations. When the strength-interval curves following both the basic driven beats and the premature ventricular depolarizations smoothly approached diastolic levels without deep dips or supernormal periods, the train of stimuli caused either occasional premature ventricular depolarizations with long coupling intervals or slow ventricular tachycardia. These relationships may participate in the initiation and the maintenance of arrhythmias.

KEY WORDS  
anodal strength-interval curves  
supernormal period  
ventricular bigeminy  
accelerating ventricular tachycardia  
myocardial infarction  
ventricular fibrillation

Inhomogeneity of recovery, impairment of conduction velocity, and ectopic pacemaker activity are known to be factors in the initiation and the maintenance of ventricular arrhythmias. The relationship between arrhythmias and excitability characteristics has received less attention. A supernormal phase in the recovery of nerves was first described by Adrian and Lucas (1) in 1912. In 1920 Adrian (2) reported a supernormal phase in isolated frog ventricle perfused with relatively acidic solutions. Characteristics of the excitability cycle of mammalian cardiac tissue were extensively studied by Orias et al. (3) in 1950. They found that ventricular strength-interval curves exhibited dips early in the cardiac cycle and supernormal periods later in the cycle. Moreover, the thresholds during the dips and the supernormal periods were sometimes lower than end-diastolic threshold levels. Dips were more prominent when anodal stimuli were used to measure the strength-interval curves than when they were cathodal stimuli were used. The major characteristics of anodal strength-interval curves are shown in Figure 1. Lewis and Master (4) in 1924 and later Ashman and Herrmann (5) and Scherf and Schott (6) used the concept of a supernormal period of excitability to explain some characteristics of atrioventricular (AV) conduction in patients with incomplete AV block. Seventeen cases of premature ventricular contractions that interrupted the T waves of the preceding beat were reported by Smirk (7) in 1949; he postulated that a supernormal period of ventricular recovery permit-
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Interpretation of the characteristics of the anodal strength-interval curve. In this example, a narrow dip is present early in the cardiac cycle and a longer supernormal period is present later in the cycle. The thresholds during both of these periods are lower than the end-diastolic threshold. Features of anodal strength-interval curves vary from animal to animal.

Methods

Experiments were carried out on 16 mongrel dogs (18-35 kg) anesthetized with sodium pentobarbital (35 mg/kg, iv). Respiration was maintained with a pump respirator: the chest was opened by a midsternal incision, and the heart was suspended in a pericardial cradle. The sinus node was crushed, a bipolar electrode was placed on the right atrial appendage, and the atrium was stimulated regularly at a cycle length of 350-500 msec. A 3-mm silver-silver chloride disk was embedded in plastic so that it could be sutured to the ventricle to maintain contact with the cardiac surface. This electrode was placed on the anterior surface of the right ventricle to determine strength-interval curves. Trains of stimuli were also delivered to the electrode. The electrode was chlorided prior to each experiment to minimize polarization. The other pole of the electrode system was a stainless steel disk implanted under the skin of the right groin. Prior to stimulation, an electrogram was recorded; if S-T segment displacement was present, the electrode was repositioned.

The stimulator used in these experiments could generate basic drive pulses, four independent delayed pulses, and a train of pulses. Any combination of pulses could be delivered as constant-current (0-100 mamp, 400-v compliance) or constant-voltage (0-100 v, 100 mamp compliance) stimuli by four optically isolated stimulus output channels. (Compliance, in this context, is the maximum value of the variable parameter for which linear output of current or voltage was obtained.) A fifth, high-resolution, constant-current output channel was used to deliver stimuli of 0-20 mamp with a resolution of 1 μamp and a compliance of 45 v.

Strength-interval curves were determined with 2-msec anodal square waves delivered to the ventricle after every seventh basic atrial driving stimulus (S1) delivered to the right atrium. In some experiments, strength-interval curves were also determined after premature ventricular depolarizations induced after every seventh S1. The premature stimulus (S2) was placed 5-10 msec later than the earliest time at which a 2-msec stimulus of twice diastolic threshold intensity could produce a propagated response. Thresholds were determined at 10-msec decrements from end-diastole to approximately the peak of the T wave and at 1-msec decrements during earlier portions of the cardiac cycle. The intensity of the test pulse was increased in 5-μamp steps until a propagated response was induced or until a level of 1.2 mamp was reached. To avoid tissue damage, stimulus intensities higher than 1.2 mamp were not used.

After strength-interval curves had been determined, arrhythmias were induced by trains of 2-msec anodal pulses. The trains of stimuli were applied for periods of up to several minutes and were delivered to the same test electrode that was used to measure the strength-interval curves. The minimum threshold to a train of stimuli was determined using a train that started immediately after the QRS complex in response to every seventh S1 and ended immediately prior to the next S1. The stimulus intensity was increased in 5-μamp steps until one or more
propagated responses occurred. After the threshold had been determined, a train of stimuli was applied. The stimulus intensity of the train was set just below the intensity of the single-cycle train that induced a ventricular response and was increased in 5-μamp steps until a ventricular arrhythmia occurred. These arrhythmias were then analyzed in terms of the characteristics of the measured strength-interval curves.

A vertical lead body surface electrocardiogram (ECG), a bipolar atrial electrogram, and a unipolar ventricular electrogram were displayed on an oscilloscope, and selected recordings were obtained. The dog was placed on a heating pad to help maintain body temperature, and femoral arterial blood pressure was monitored. The stability of the preparation was evaluated by repeating measurements at selected points in the strength-interval curves several times during the course of the experiments.

Results

Three types of arrhythmias occurred in response to the trains of stimuli. Each type was associated with a particular form of the strength-interval curve. Stable ventricular bigeminy occurred if the diastolic threshold following premature ventricular depolarizations was higher than the diastolic threshold of the basic atrial driven beats. An accelerating ventricular tachycardia developed when the minimum threshold appeared as deep dips following both the basic driven beats and the premature depolarizations. The third type of response consisted of occasional premature beats with long coupling intervals that sometimes alternated with a ventricular tachycardia at a cycle length close to the coupling interval of the premature beats. When this type of arrhythmia occurred, deep dips and supernormal periods were not seen in the strength-interval curves of either the basic driven beats or the premature ventricular depolarizations.

STABLE VENTRICULAR BIGEMINY

Stable ventricular bigeminy occurred on six occasions in response to trains of low-intensity stimuli. On three occasions, strength-interval curves were measured following premature ventricular depolarizations as well as following the basic driven beats. Tracings from one dog with this form of arrhythmia and the associated strength-interval curves are shown in Figure 2. The minimum threshold after the atrial driven beat, 520 μamp, occurred during the supernormal phase and was 20–30 μamp less than the end-diastolic threshold. The lowest level of the dip was 720 μamp. Following the premature ventricular depolarization the threshold level at the lowest point in the dip was 580 μamp, and during the supernormal phase it was 660 μamp. Both of these levels were higher than the threshold during the supernormal period following the atrial driven beat. A train of stimuli with an intensity of 530 μamp, that is, an intensity slightly above the threshold level of the supernormal phase of the atrial driven beats but below the minimum threshold of the ventricular premature beats, induced a stable ventricular bigeminy. Possibly the train of stimuli induced a ventricular response during the supernormal phase of the atrial driven beat but was ineffective following the premature ventricular depolarization because of the higher threshold after it. Stable ventricular bigeminy in response to trains of anodal stimuli occurred only in association with this combination of forms of the strength-interval curves. The range of stimulus intensities over which bigeminy could be induced was narrow (5 to 10 μamp). Continued increases in the intensity of the train of stimuli above the level that induced bigeminy induced ventricular fibrillation.

ACCELERATING VENTRICULAR TACHYCARDIA

Accelerating ventricular tachycardia occurred in nine experiments, and strength-interval curves were determined after premature ventricular depolarizations as well as after basic driven beats in six of these. Tracings from one dog and the associated strength-interval curves are shown in Figure 3. Deep wide dips in the strength-interval curves followed both the basic atrial driven beats and the premature ventricular depolarizations. The dip associated with the premature ventricular depolarization was deeper than the dip associated with the atrial driven beat. With both depolarizations, the thresholds at the lowest points of the dips were less than end-diastolic thresholds. A train of stimuli with an intensity of 970 μamp, that is, an intensity between the minimum threshold levels of the atrial driven beat and the premature ventricular depolarization, induced an accelerating ventricular tachycardia. It is not known why stimuli with intensities less than the measured minimum threshold for the atrial driven beat were capable of producing a ventricular response. However, once a response occurred, the train induced an accelerating ventricular tachycardia, as would be expected, with capture occurring during the dip of each of the subsequent beats. Another example of this type of arrhythmia and the associated strength-interval curves is shown in Figure 4. In this dog accelerating ventricular tachycardia degenerated to ventricular fibrillation after only a few cycles. As in Figure 3, the thresholds during the dips of both the basic

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A: Atrial and ventricular electrograms recorded during the application of a train of anodal stimuli. The first complex in the ventricular electrogram is the response to the basic drive delivered to the atrium, and the second complex is a ventricular depolarization in response to the train of stimuli. The resulting rhythm is ventricular bigeminy. The electrograms have been retouched. B: Strength-interval curves following basic driven beats and induced premature ventricular depolarizations (PVD). The minimum threshold in the strength-interval curves was a shallow supernormal period (arrow) at 300-310 msec following the basic driven beat. The minimum threshold following the induced premature ventricular depolarization was higher than that following the basic driven beat. The $S_1$-$S_2$ cycle length was 400 msec, and the $S_1$-$S_3$ interval for the induced premature ventricular depolarization was 310 msec. The horizontal line on the graph indicates the stimulus intensity of the train of anodal stimuli that induced the arrhythmia shown in A. The same format of electrograms and strength-interval curves is used in Figures 3-5.

atrial driven beats and the premature ventricular depolarizations were lower than the end-diastolic thresholds. In dogs with this combination of strength-interval curves, stable ventricular bigeminy could never be obtained with trains of stimuli. Accelerating ventricular tachycardia always occurred and was frequently followed by ventricular fibrillation.

PREMATURE DEPOLARIZATIONS WITH LONG COUPLING INTERVALS AND SLOW VENTRICULAR TACHYCARDIA

On four occasions premature ventricular depolarizations with long coupling intervals and slow ventricular tachycardias occurred in response to trains of stimuli. Strength-interval curves were determined following premature ventricular depolarizations as well as following the atrial driven beats on all four occasions. An example of this form of arrhythmia and the associated strength-interval curves is shown in Figure 5. Dips were present following both the basic driven beats and the induced premature ventricular depolarizations, but the thresholds during these dips were much higher than the end-diastolic thresholds. Supernormal periods were absent following both beats, and end-diastolic thresholds were the same following both beats. Such strength-interval curves differ from those associated with accelerating ventricular tachycardia and fibrillation, because the dips following the basic driven beats and the premature ventricular depolarizations in the latter have minimum thresholds lower than the end-diastolic thresholds.
FIGURE 3

A: Electrograms showing accelerating ventricular tachycardia in response to a train of anodal stimuli.
B: Strength-interval curves following basic driven beats and induced premature ventricular depolarizations (PVD). There are deep dips in the strength-interval curves following both the basic driven beats and the induced premature ventricular depolarizations. The S₁-S₂ cycle length was 400 msec and the S₂-S₃ interval was 270 msec.

Discussion

These experiments demonstrate a relationship between the form of anodal strength-interval curves and the type of arrhythmia that results from trains of low-intensity anodal stimuli. It is postulated that the trains of stimuli produce responses at the minimum threshold levels of the strength-interval curves. The graph in Figure 6 supports this hypothesis. The minimum thresholds of the strength-interval curves are plotted along the hori-
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Horizontal axis, and the minimum intensities of single-cycle trains that produced a ventricular depolarization are plotted along the vertical axis. If the trains of stimuli operated in the postulated way, there should be a one-to-one relationship between these two values. With few exceptions, such a relationship was found, indicating that trains of stimuli applied for long periods of time produce responses at the minimum threshold of each cycle if the intensity of the train is greater than the minimum threshold occurring in that cycle.

It is not clear why some dogs have one form of strength-interval curve and others have a different form. Several factors including variations in acid-base balance (2), electrolyte balance, or level of barbiturate anesthesia (11) have been reported to influence the form of the strength-interval curve. In three dogs in the present study, the strength-interval curves lost deep dips and supernormal periods after the administration of supplemental doses of sodium pentobarbital. After this loss occurred, slow ventricular tachycardia was induced by trains of stimuli. Two of these dogs had exhibited accelerating ventricular tachycardia and fibrillation in response to trains of stimuli prior to the administration of additional anesthesia, and the other dog had exhibited stable ventricular bigeminy.

The relationship of experimental anodal stimulation to spontaneously occurring arrhythmias is not known. There is evidence that anodal currents can provide effective stimuli (12-14); the work of Harris and Moe (9) has shown that anodal current

![Figure 4](image)

A: Electrograms showing the onset of ventricular fibrillation in response to a train of anodal stimuli. B: Strength-interval curves following basic driven beats and induced premature ventricular depolarizations (PVD). There are deep dips in the strength-interval curves following both the basic driven beats and the induced premature ventricular depolarizations. The S1-S2 cycle length was 400 msec and the S1-S2 interval was 340 msec.
more effectively induces fibrillation than does cathodal current. The relationships described in the present paper may have counterparts in patients with ventricular arrhythmias, especially arrhythmias associated with myocardial infarction where differences in resting membrane potentials and action potential duration between ischemic and nonischemic tissue may provide a source of anodal current. Evaluation of the magnitude of currents of injury and the number of leads in which they appear in clinical electrocardiograms is frequently used as a measure of prognosis and severity of myocardial infarction (15, 16) and as a measure of infarct size (17). The most specific implication of the participation of these “currents of injury” in the initiation of ventricular fibrillation has been offered by Brooks et al. (18). These authors state that the occurrence of fibrillation can be most readily explained by the assumption that provocative agents such as local injury or localized anoxia create unequal effects on cardiac tissue. We propose that the inhomogeneity of properties between ischemic and nonischemic tissue is not only appropriate for sustaining ventricular arrhythmias and fibrillation but may also be capable of initiating ventricular arrhythmias and fibrillation. The marked alterations in conduction associated with infarction would be expected to maximize the difference in properties between ischemic and nonischemic tissues and further enhance the likelihood of the initiation and the maintenance of ventricular arrhythmias. The results of the present...
study suggest that, in addition to inhomogeneity of conduction and recovery and abnormalities of automaticity, the excitability characteristics reflected in the strength-interval curves also influence vulnerability to arrhythmias. For example, if deep dips are present, vulnerability to fibrillation would be expected to be greater than would be the case if the strength-interval curves smoothly approached end-diastolic levels. The possibility that drug therapy directed at controlling the form of the strength-interval curve can be used to treat arrhythmias has important therapeutic implications and should be further investigated.

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