Factors Related to the Induction of Ventricular Fibrillation in the Normal Canine Heart by Programmed Electrical Stimulation

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Programmed electrical stimulation was performed in eight normal dogs using a stimulator and endocardial electrode catheters identical to those used in human studies. The right and left ventricular apex were paced at a drive cycle length of 400 ms and, in some cases, 500 ms, with a pacing sequence of single \(S_1S_2\), double \(S_1S_2S_3\) and triple \(S_1S_2S_3S_4\) premature impulses introduced after eight paced complexes. Pacing sequences were performed using combinations of pulse width (1, 2 and 4 ms) and current strengths of 2, 5 and 10 times diastolic threshold, and in three dogs, 15 times diastolic threshold.

Twenty-two episodes of ventricular fibrillation were initiated in five dogs in 170 pacing sequences using current strengths up to 10 times diastolic threshold, and six episodes of ventricular fibrillation in the two of three remaining dogs tested at 15 times diastolic threshold. Ventricular fibrillation was reproducible on seven of nine occasions. Ventricular fibrillation was never induced by \(S_1S_2\) at up to 15 times diastolic threshold, and in three dogs, 15 times diastolic threshold.

S_1S_2S_3 at 10 or more times diastolic threshold. Induction of ventricular fibrillation was not related to pulse width, but when sequences using \(S_1S_2S_3\) at 10 times diastolic threshold were examined, ventricular fibrillation was related to the shortness of the coupling intervals of the premature stimuli \(S_1S_2 + S_2S_3 + S_3S_4\): ventricular fibrillation \(= 367 \pm 26\) ms, no ventricular fibrillation \(= 417 \pm 41\) ms, \(p < 0.001\). Current strength appeared to have some independent role, occasionally causing ventricular fibrillation at 10 times but not at 5 times diastolic threshold at similar coupling intervals.

It is concluded that spurious ventricular fibrillation is unlikely to be initiated in the normal canine ventricle by \(S_1S_2\) at up to 15 times diastolic threshold, or by \(S_1S_2S_3\) at less than 10 times diastolic threshold. \(S_1S_2S_3\) appeared capable of initiating ventricular fibrillation at any current strength, with maximal frequency at 10 times diastolic threshold or greater. These findings allow better assessment of the significance of arrhythmias induced by these pacing methods in abnormal canine hearts, and demonstrate some principles that may be applicable to human studies.

Programmed electrical stimulation, whereby the heart is paced by timed electrical impulses, has become an important tool for studying the vulnerability of the heart to ventricular arrhythmias in a variety of pathologic situations. It has not only been useful for studying the arrhythmogenic properties of animal models of myocardial ischemia and infarction (1), but also has become accepted as a useful method for initiating and studying ventricular arrhythmias in susceptible human beings (2).

When any new clinical test is introduced, its sensitivity and specificity must be clearly defined. For programmed electrical stimulation in human beings, this means that the technique must have sensitivity, to enable it to induce ventricular arrhythmias in patients known to be susceptible to them, and specificity, so that these arrhythmias are in accord with previous clinical experience. Specificity also implies that clinical meaning can be attached to ventricular arrhythmias induced by programmed electrical stimulation in patients who do not have a definite history of arrhythmias.
Similar principles also apply to animal studies, as demonstrated by Brooks et al. (3), who showed that normal canine hearts are prone to ventricular fibrillation in response to a single suprathreshold electrical stimulus.

Currently, methods employed for programmed electrical stimulation vary quite widely among medical centers (4). Improved sensitivity has been claimed for the use of multiple premature extrastimuli to induce ventricular arrhythmias, as well as for testing at multiple ventricular pacing sites (for example, left as well as right ventricle). In addition, closer coupling of these premature stimuli, believed to be important in inducing some ventricular arrhythmias, can be achieved by increasing the current strength (5) and by altering the duration of the rectangular pulse wave delivered by the stimulator (6). Ultimately, however, one could reach a stage where these methods might result in the induction of sustained ventricular arrhythmias, particularly ventricular fibrillation, in a normal heart with no predisposition to arrhythmias, thereby destroying any specificity of the test.

The purpose of this study was to explore the limits of programmed stimulation in the normal canine ventricle when newer testing methods such as increased current strength, alterations in pulse width and changes in pacing site were added to a conventional pacing protocol using multiple premature stimuli. We believed the results of such a study would provide useful data by which to judge the results of programmed stimulation in abnormal situations, for example, closed chest dog models of ischemic heart disease. Because it would be unethical to test the limits of programmed electrical stimulation in normal human subjects, we also hoped the data would provide some guidelines as to what forms of programmed stimulation are most likely to produce meaningful results in clinical studies.

Methods

Experimental preparation. Electrophysiologic studies were performed on eight healthy mongrel dogs (19.5 to 25.3 kg). The day before a study, general anesthesia was induced with 20% ethyl carbamate (50 to 100 ml intravenously) and two 6 French bipolar USCI electrode catheters (1 cm interelectrode distance) were inserted into each dog via neck vessels, and positioned at the apex of the left and right ventricle, respectively. The position of the catheters was confirmed fluoroscopically, and they were secured in the vessels by suturing. A catheter was positioned in a carotid artery for arterial pressure monitoring.

On the day of the study, each dog was sedated with 1 mg/kg of intramuscular morphine sulfate, and was secured lying on its right side in a cradle in a quiet and dimly lit room. Morphine sulfate was used in light of our previous experience that the sedative properties of diazepam were quite unsatisfactory over the several hours required to perform a study. However, the nonaversive environment we maintained during these studies probably led to no significant effects of the morphine on the ventricular fibrillation threshold (7).

Pacing by means of the electrode catheters was performed using a programmable stimulator (Bloom Associates, Ltd.), identical to that used for our human studies. The calibration of the pulse width and current strength was checked and adjusted if necessary before the studies. The maximal current available for stimulation was 20 mA. Surface electrocardiograms, arterial pressure and intracardiac recordings from the pacing electrode other than that being used for pacing were amplified using an Electronics for Medicine DR 16 system, and recorded on magnetic tape (Bell & Howell data tape CPR 4010) for selective retrieval on paper at speeds of 50 to 100 mm/s.

Pacing protocol. The pacing protocol consisted of a sequence of single \((S_1,S_2)\), then double \((S_1,S_2,S_3)\) and finally triple \((S_1,S_2,S_3,S_4)\) premature ventricular stimuli after eight ventricular paced complexes \((S_1)\) at a cycle length of 400 ms. In five dogs, a cycle length of 500 ms was also used. The protocol was performed in a conventional manner, scanning diastole in 10 ms decrements with the last of the premature stimuli, keeping any preceding premature stimuli within 20 ms of the ventricular refractory period. Pacing was performed twice at each set of coupling intervals. Four seconds were allowed to elapse between periods of pacing, equivalent to three or four sinus beats at the spontaneous heart rates of 90 to 120 beats/min after resumption of sinus rhythm.

Each of these pacing sequences was performed at the left and right ventricular apex, at a current strength equal to 2, 5 and 10 times, and, in three dogs, at 15 times diastolic threshold, and at pulse durations of 1, 2 and 4 ms. Excluding data obtained at 15 times diastolic threshold, this resulted in pacing sequences using 18 possible combinations of pacing sites, current strength and pulse duration. The pacing protocol was necessarily modified by the fact that if ventricular fibrillation occurred, some limit would have to be placed on the number of times fibrillation and defibrillation occurred, as the latter may cause myocardial necrosis if used repeatedly (8). Thus, although the order of the combinations of variables used varied from one dog to another, it was decided that 1) if a certain combination frequently caused ventricular fibrillation in initial studies, it would preferentially be tested last in later studies to obtain maximal information from each animal, and 2) if ventricular fibrillation occurred with fewer than three premature stimuli or less than the maximal current strength to be tested with a certain set of variables, that part of the protocol would not be pursued further as we would assume that ventricular fibrillation would also occur at higher "stress" levels.

Cardiac tissue findings. Seven of the eight dogs were sacrificed after the experiments. Macroscopic examination
of the cardiac tissues revealed no evidence for heart worms or myocardial necrosis.

Statistical analysis. Data were compared between groups using one of the following nonparametric tests (9): Friedman's analysis of variance, Mann-Whitney U test and Wilcoxon matched-pairs signed-rank test. The test used in each case is given next to the probability (p) value in the text. A p value of 0.05 or less was considered significant.

Results

Excluding data using 15 times diastolic threshold, the 18 combinations of pacing variables at drive cycle lengths of either 400 or 500 ms resulted in 170 pacing sequences being tested in the dogs (Fig. 1). A complete protocol, consisting of the use of the 18 combinations of pacing variables at one of the two drive rates, was performed in three dogs. However, even though some combinations were tested at more than one drive rate, between 3 and 12 of the 18 pacing combinations were omitted in the remaining five dogs owing to technical difficulties (for example, catheter displacement, current requirements exceeding 20 mA) or for reasons already given (such as the induction of ventricular fibrillation with a given set of other variables at a lower current strength than the maximum for the protocol) or because six or seven episodes of ventricular fibrillation had already been initiated in a dog and myocardial damage from repeated defibrillation may have occurred if testing was continued. The net result was that each combination of variables was tested in a pacing sequence in at least four of the dogs, and on average, in six dogs.

Diastolic threshold. The diastolic threshold at 1 ms pulse width ranged from 0.4 to 1.7 mA (mean 0.5) in the right ventricle (eight dogs), and from 0.4 to 3.6 mA (mean 1.6) in the left ventricle (seven dogs). The slightly increased mean threshold in the left ventricle may have reflected some displacement and less secure position of the catheter placed in the endocardium 24 hours before testing; in one dog the catheter had become completely dislodged and could not be replaced without reoperation on the neck.

Ventricular arrhythmias. Ventricular fibrillation. This was induced by a combination of pacing variables using current strengths up to 10 times diastolic threshold in five of the eight dogs. Two of the three remaining dogs were subsequently tested using 15 times diastolic threshold (see later). Twenty-two episodes of ventricular fibrillation occurred and, in addition, reproducibility of induction of ventricular fibrillation for a given set of variables was randomly tested on nine occasions in four dogs. Ventricular fibrillation was reproduced in seven of the nine tests. During reproducibility tests, it was noted that although other pacing variables were kept constant, the coupling intervals required to induce ventricular fibrillation on the second occasion varied slightly (Fig. 2). Failure to reproduce ventricular fibrillation

![Figure 1](image-url)
in one of the two negative reproducibility tests may have been due to an inability to get within 20 ms of the same short coupling intervals that initially induced the arrhythmia. To test a hypothesis used to restrict the pacing protocol (see Methods), S1S2S3S4 was used in a pacing sequence in which S1S2S3 had already produced ventricular fibrillation, and ventricular fibrillation was again induced. Similarly, pacing at 15 times diastolic threshold reproduced ventricular fibrillation in one sequence when it had already occurred at 10 times diastolic threshold.

Ventricular tachycardia. Sustained uniform or multiform ventricular tachycardia was never induced. Occasionally, one or two nonstimulated ventricular complexes or runs of nonsustained ventricular tachycardia (less than 10 complexes) were seen, the latter usually a prelude to the induction of ventricular fibrillation at the same or similar coupling intervals (Fig. 3).

Defibrillation. When ventricular fibrillation occurred and the dog became unconscious, external defibrillation was successfully employed on each occasion using a single shock of either 160 or 200 joules (measured output of the defibrillator). The dog was then allowed to recover for 10 to 15 minutes before pacing was recommenced, allowing pulse rate and blood pressure to return to basal levels.

Effects of pacing variables on the initiation of ventricular fibrillation. Figure 4 summarizes the findings pertinent to the relation of pacing site, pulse width and number of premature stimuli on the induction of ventricular fibrillation, and the following observations pertain to it. Pacing site and pulse width were selected at random, but high current strengths were tested last, after experience in the first two dogs suggested that they might predispose to ventricular fibrillation.

Pacing site. Ventricular fibrillation occurred during 14 (15.6%) of the 90 pacing sequences performed from the apex of the right ventricle, nearly twice as often as occurred during left ventricular pacing (8 [8.8%] of 80 sequences). This difference reached statistical significance (Wilcoxon matched-pairs signed-rank test, p < 0.05), even though there were no significant differences in ventricular refractory periods or shortest coupling intervals achievable (Wilcoxon matched-pairs signed-rank test). On average, the left ventricular effective refractory period was shorter by 15 and 23 ms, respectively, in two dogs, but longer by 14 to 43 ms in five dogs (refractory periods could not be compared in one dog). Similar trends were seen in coupling intervals.

Pulse width. The frequency of occurrence of ventricular fibrillation was not related to the pulse width used. Ventricular fibrillation occurred in 7 (13%) of 54 sequences at 1 ms, 9 (14.5%) of 62 sequences at 2 ms and 6 (11.1%) of 54 sequences at 4 ms.

Number of premature stimuli. Ventricular fibrillation was never induced by S1S2 tested on 170 occasions at either pacing site, and using any combination of pulse width and current strength up to 10 times diastolic threshold. Three episodes of ventricular fibrillation occurred with S1S2S3 (3 [1.8%] of 170 sequences). The remaining 19 episodes occurred with S1S2S3S4 (19 [11.4%] of 167 sequences), excluding the 3 sequences in which ventricular fibrillation had already occurred with S1S2S3.

Pacing current strength. Only one episode of ventricular fibrillation was induced using a current strength equal to two times diastolic threshold (1 [1.6%] of 64 sequences). Three episodes of ventricular fibrillation occurred using 5 times diastolic threshold (3 [6%] of 50 sequences) and 18 episodes occurred at 10 times diastolic threshold (18 [32%]

Figure 2. Same dog as in Figure 1. Initiation of ventricular fibrillation and its reproducibility. The recordings are arranged in a similar manner. A, After a series of paced complexes (S1V1) at a drive cycle length of 500 ms (2 ms pulse width, 10 times diastolic threshold), S1S2S3S4 at the right ventricular apex initiates ventricular fibrillation (VF). V4 is fractionated as in Figure 1, and S4 occurs before the left ventricle has fully depolarized from S3 (S4 precedes V3 at the left ventricular [LV] apex). Additional nondriven fractionated complexes are seen after V4, followed by a brief period of noncontinuous, relatively organized activity before ventricular fibrillation with continuous electrical activity occurs. B, Results of pacing several minutes later after the dog had recovered from electrical cardioversion. Similar coupling intervals again resulted in ventricular fibrillation, all other variables remaining unchanged.

A)

B)

Figure 2. Same dog as in Figure 1. Initiation of ventricular fibrillation and its reproducibility. The recordings are arranged in a similar manner. A, After a series of paced complexes (S1V1) at a drive cycle length of 500 ms (2 ms pulse width, 10 times diastolic threshold), S1S2S3S4 at the right ventricular apex initiates ventricular fibrillation (VF). V4 is fractionated as in Figure 1, and S4 occurs before the left ventricle has fully depolarized from S3 (S4 precedes V3 at the left ventricular [LV] apex). Additional nondriven fractionated complexes are seen after V4, followed by a brief period of noncontinuous, relatively organized activity before ventricular fibrillation with continuous electrical activity occurs. B, Results of pacing several minutes later after the dog had recovered from electrical cardioversion. Similar coupling intervals again resulted in ventricular fibrillation, all other variables remaining unchanged.
of 56 sequences). The incidence of ventricular fibrillation induction was significantly related to the amount of pacing current used (Friedman analysis of variance, \( p < 0.01 \)).

In addition, 15 pacing sequences were tested using current strength 15 times diastolic threshold in three dogs. Ventricular fibrillation occurred in all three dogs, a total of six times (40%), but all once with \( S_1S_2S_3S_4 \); this included ventricular fibrillation induction in two dogs in which no ventricular fibrillation had been induced by any sequence using up to 10 times diastolic threshold. In the third dog, ventricular fibrillation was reproduced with a combination of variables that had already produced ventricular fibrillation at 10 times diastolic threshold \( (S_1S_2S_3S_4, \text{2 ms pulse duration, right ventricular apex}) \), or induced with a combination of pulse width and pacing site that had failed to induce ventricular fibrillation at 10 times diastolic threshold \( (S_1S_2S_3S_4, \text{2 or 4 ms, right and left ventricle}) \).

The combination of \( S_1S_2S_3S_4 \) and a current strength of 10 times diastolic threshold produced ventricular fibrillation on 15 occasions (15 [28.8%] of 52 sequences). This percent reaches 33.9% if one includes four instances in which ventricular fibrillation had occurred with \( S_1S_2S_3S_4 \) at 5 times diastolic threshold or occurred with \( S_1S_2S_3 \) at 10 times diastolic threshold, and one assumes that it would have occurred with \( S_1S_2S_3S_4 \) stimuli and 10 times diastolic threshold had it been tested. Twenty of 28 episodes of induced ventricular fibrillation occurred with \( S_1S_2S_3S_4 \) at 10 times diastolic threshold or greater.

**Coupling intervals of premature stimuli.** We found that ventricular fibrillation usually occurred with coupling intervals of the premature stimuli just outside the effective refractory period. The use of a basic drive cycle length of 400 ms produced coupling intervals that, when compared with 500 ms were slightly shorter \( (S_1S_2: 0 \text{ to } -25 \text{ ms, mean } -12); S_2S_3: +40 \text{ to } -30 \text{ ms (mean 9); } S_2S_4: +50 \text{ to } -40 \text{ ms (mean } -8). \) This appeared to make no significant difference. However, had we tested wider \( S_1S_1 \) cycle lengths, significant differences in the refractory periods probably could have occurred.

To test the hypothesis that the ability to achieve short coupling intervals predisposes to ventricular fibrillation, we compared the coupling intervals at drive cycle lengths of
400 or 500 ms that resulted in the 15 episodes of ventricular fibrillation induced by S1S2S3S4 at 10 times diastolic threshold with the shortest coupling intervals seen with 39 completed pacing sequences at 10 times diastolic threshold when S1S2S3S4 did not result in ventricular fibrillation. Because a third premature stimulus itself increased the incidence of induced ventricular fibrillation, we first compared the coupling interval of the third premature stimulus (S3S4) in sequences with and without ventricular fibrillation. Essentially there was no significant difference (Ventricular fibrillation: 97 ± 20 ms; no ventricular fibrillation: 100 ± 25 ms, Mann-Whitney U test). However, when the sums of the coupling intervals (S1S2 + S2S3 + S3S4) were compared, they were significantly shorter when ventricular fibrillation was induced (367 ± 26 ms) than when it was not (417 ± 41 ms) (Mann-Whitney U test, p ≤ 0.001). This was due to significant differences in S1S2 and S2S3 coupling intervals, predisposing to the induction of ventricular fibrillation by S4. (S1S2, ventricular fibrillation: 154 ± 15 ms, no ventricular fibrillation: 184 ± 19 ms; S2S3, ventricular fibrillation: 117 ± 17 ms, no ventricular fibrillation: 138 ± 14 ms, Mann-Whitney U test, p < 0.001).

Furthermore, close coupling intervals frequently resulted in S4 capturing the apex of the paced ventricle before the apex of the opposite ventricle had even been depolarized by the previous premature stimulus (S1 (Fig. 2). This rapid sequence of impulses appeared to predispose to ventricular fibrillation (Fig. 2).

Independent role of pacing current. The fact that a combination of increased current strength and S1S2S3S4 was the most frequent cause of ventricular fibrillation could be explained solely on the basis that the increased current strength allowed maximal shortening of the coupling intervals of the premature stimuli. However, we found evidence that the pacing current itself may have a role in inducing ventricular fibrillation independent of the number of premature stimuli and their coupling intervals. Usually the sum of the shortest coupling intervals achieved at one current strength was more than 10 ms greater than that resulting in ventricular fibrillation at a higher current, all other factors remaining equal. The reproducible induction of ventricular fibrillation at high current strengths but not at lower currents at almost identical coupling intervals on four separate occasions in three dogs suggests an independent role of the pacing current. Figure 5 shows such an example in one of the dogs.

Discussion

This study shows that ventricular fibrillation can be initiated in the normal canine heart by programmed stimulation using a clinical protocol, particularly when S1S2S3S4 are used at current strengths in excess of 2 times diastolic threshold. It appears as if the achievement of short coupling intervals, overall rather than just for the third premature stimulus, was necessary for the induction of ventricular fibrillation, but current strength itself appeared also to have some independent role.

Dispersion of refractoriness as a mechanism of ventricular fibrillation. Previous studies (10) on the mechanisms of ventricular fibrillation and its electrical induction in the canine heart have indicated that ventricular fibrillation both in normal and abnormal ventricles is probably due to a critical dispersion of refractoriness. Electrical induction of ventricular fibrillation appears to depend on elevating the basal level of dispersion of refractoriness to this critical level. Several factors could increase the dispersion of refractoriness. These include:

1) Heart rate. The effects of heart rate on dispersion of

![Figure 5](image-url)
refractoriness is controversial, appearing to be directly proportional in a study of left ventricular epicardial pacing by James et al. (11), yet quite the opposite (maximal at slowest heart rates) in an earlier study using right ventricular epicardial pacing by Han et al. (12).

2) Premature impulses. If a premature impulse is introduced after a period of sinus rhythm or fixed rate atrial or ventricular pacing, the effective refractory period will shorten (13) and the dispersion of refractoriness during repolarization after the premature impulse will be greater than during the preceding rhythm (14). The increase in dispersion of refractoriness and shortening of refractory periods is maximal close to the point of stimulation rather than distant from it (14,15), and may reflect a local effect at the pacing site in addition to prematurity (14).

3) Sequential, closely coupled premature stimuli. These may interact by summation or inhibition to increase or diminish dispersion of refractoriness (16).

4) Stimulating current. An increase in the pacing current will increase the dispersion of refractoriness after a ventricular depolarization (17). In addition, increasing the stimulating current shortens the effective refractory period of the ventricle at the pacing site, allowing premature stimuli to capture the ventricle at closer coupling intervals than before (18).

5) Site of pacing. The right ventricle has been thought to be more vulnerable to ventricular fibrillation than the left (19). However, this finding has been based on studies using epicardial pacing, and a recent study (20) comparing endocardial pacing sites in the right or left ventricle has not confirmed this. The site of stimulation, however, can be very important in an abnormal heart. The proximity of the site of stimulation to the site of reentry in the abnormal region of the heart, as well as the refractory period and the conduction properties of the tissue between the site of stimulation and the site of reentry may play an important role in the inducibility of ventricular arrhythmias or the lack of it.

Comparison with previous studies. Any one or several of these factors could have been responsible for the induction of ventricular fibrillation in the present study. Previous studies of ventricular fibrillation in animal models differ in many ways from our study. Predominantly, previous studies have used open chest dogs anesthetized with sodium pentobarbital or an equivalent anesthetic, and have paced the epicardial surface of the heart. Sodium pentobarbital anesthesia is known to protect the heart from ventricular fibrillation (21), yet open chest dogs may gradually develop metabolic acidosis, lowering the ventricular fibrillation threshold (10). However, Wetstein et al. (22) recently studied 10 normal open chest dogs maintaining normal pH, arterial partial pressure of oxygen (P02) and arterial partial pressure of carbon dioxide (PCO2) and found that ventricular fibrillation could be induced by S1S2S3 (two times diastolic threshold, 2 ms pulse duration) in 40% of the dogs, and by S1S2S3S4 in all of the dogs. The higher incidence of ventricular fibrillation in this study could have been caused by increased circulating plasma catecholamines induced by operative stress in the open chest preparations (23).

Although an increase in pulse width, with an otherwise fixed set of variables, can shorten ventricular refractoriness (6), pulse width did not appear to be an important factor in our study, perhaps because its magnitude in normal tissues was overshadowed by the effects of current strength and prematurity.

An exact quantitative comparison is impossible because of variation in technique, but it is interesting to note that currents required for a single premature stimulus to initiate ventricular fibrillation during ventricular drive pacing of the right ventricular endocardium in normal dogs was found to be 27 ± 10 mA by Gang et al. (24), and 35.6 ± 1.7 mA in a study by Matta et al. (25). The maximal current used in our canine studies was 20 mA, and a single premature stimulus of either the left or the right ventricular apex never initiated ventricular fibrillation. Two premature stimuli initiated ventricular fibrillation 1.8% of the times it was tested, at current strengths ranging from 2.5 to 20 mA. Judging by previous reports (26) on the current required to induce repetitive ventricular responses by two premature stimuli, ventricular fibrillation may only be induced with much higher currents. Finally, Fisher et al. (27) studied the effects of single, double and triple premature ventricular stimuli at two to four times the diastolic threshold in 30 dogs without producing any significant ventricular arrhythmias.

We found that endocardial pacing initiated ventricular fibrillation more often from the right ventricular apex than from the left ventricular apex despite insignificant differences in refractory periods and coupling intervals. This contrasts with the findings of Horowitz et al. (20) that ventricular fibrillation thresholds to endocardial pacing in the ventricles are equivalent. However, we feel that because in one of our dogs ventricular fibrillation was initiated seven times in the right ventricle and the left ventricle could not be paced in a stable manner and was thus not tested, our finding may be biased and not generally applicable.

The use of intense repetitive electrical countershock to the canine heart has been reported to cause myocardial necrosis (26). However, the energies we used to successfully defibrillate our animals were less than those used in that report, and only two animals had more than five defibrillations. There was no instance when a dog appeared to be vulnerable to an unexpectedly low degree of pacing "stress" after several countershocks, and each animal was allowed to recover and return to a heart rate and blood pressure approximating the control value before the pacing protocol continued. We therefore believe that subsequent indications of ventricular fibrillation are caused by pacing itself rather than by a possible cardioversion-induced ventricular damage.
Implications for human studies. Previous work in human beings has shown that, using conventional variables, such as twice diastolic threshold current and a pulse width of 1 or 2 ms for pacing, ventricular fibrillation is virtually never induced by a single premature stimulus during ventricular pacing, even in patients with a clinical predisposition (28). These findings are similar to our present experimental results.

However, we are uncertain as to the relevance and applicability of induced ventricular fibrillation with $S_2S_3S_4$ stimulation in the normal canine ventricle to human ventricles. This is so because: 1) the induction of ventricular fibrillation in our experiment is uncommon in patients by the present methods of pacing; 2) both the size and the geometry of human ventricles are different from those of canine ventricles, and these may importantly influence the occurrence of induced ventricular fibrillation (29); and 3) the minimal coupling intervals achievable in human beings are found consistently to be longer than those in the dogs reported in this study regardless of whether there was clinical evidence for abnormality in the ventricles or not. Although the exact relation between prematurity and increases in the dispersion of refractoriness may be quite different between human and canine ventricles, human ventricles may have some inherent protection against ventricular fibrillation induced by ventricular pacing.

Implications for future studies. We feel that one implication of this study for future research in animal arrhythmia models is that $S_2S_3$ stimulation is not likely to cause spurious ventricular fibrillation at current strengths of up to 15 times diastolic threshold, in accordance with previous studies (24,26). $S_2S_3S_4$ stimulation appeared relatively benign at 2 and 5 times diastolic threshold, but may not be at 10 times diastolic threshold. $S_2S_3S_4$ stimulation can induce ventricular fibrillation at any current strength, although the frequency does not become appreciable until current 10 times diastolic threshold is used. Further, we believe that when higher stimulating currents are used, they should be calibrated with reference to the diastolic threshold, rather than using absolute amounts, because evidence from animal studies (30) suggests that the diastolic threshold may relate to the ventricular fibrillation threshold.

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References


