Day-to-day variations in inducibility of ventricular tachyarrhythmias during the late postmyocardial infarction phase in conscious dogs

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ABSTRACT The inducibility of ventricular tachyarrhythmias was studied daily on days 3 through 8 after experimental myocardial infarction in 15 conscious dogs. Although a sustained ventricular tachyarrhythmia was produced on one or more occasions in 11 of 15 dogs (73%), there was marked daily variation in the results of programmed stimulation. Ventricular fibrillation or sustained ventricular tachycardia was elicited in six dogs on day 3 after infarction. In two of these dogs, no sustained tachycardia could be induced by day 7. In nine dogs sustained ventricular arrhythmias were not inducible on day 3. By day 6 to 7, sustained ventricular tachycardia was inducible in five of these dogs. In clinical practice similar variation in the inducibility of sustained ventricular arrhythmias may conceivably complicate the use of results of programmed ventricular stimulation as determinants of risk of sudden death after myocardial infarction.


THERE HAS BEEN considerable recent interest in the possibility of identifying patients at risk of sudden death after recovery from acute myocardial infarction. An invasive approach to prognostic evaluation involves the use of programmed ventricular extrastimulation 1 to 4 weeks after recovery to determine whether ventricular arrhythmias are inducible.1–3 Inducible ventricular tachycardia appears to require a substrate of areas of electrophysiologically depressed, slowly conducting myocardium, usually at the border of the infarcted area.4,5 These areas confer chronic “electrical instability,” with its attendant risk of malignant arrhythmias. We have studied the day-to-day variability in the results of programmed ventricular stimulation in conscious dogs after experimental myocardial infarction to determine whether major changes in the inducibility of ventricular arrhythmias are to be expected in the early postinfarction period. We have also investigated the possible influence of resting sinus cycle length and ventricular effective refractory period on the outcome of programmed stimulation.

Methods

Mongrel dogs (11 to 24 kg) were premedicated with morphine and chlorpromazine and anesthetized with pentobarbital (15 mg/kg). After induction of anesthesia, 1 meq/kg benzyl penicillin and 30 mg/kg methylprednisolone were given intravenously.6 The surgical technique of two-stage proximal ligation of the left anterior descending coronary7 and implantation of atrial and ventricular bipolar stimulating electrodes and subcutaneous electrocardiographic electrodes has recently been described in detail.8

Fifteen dogs were studied with programmed stimulation over 3 to 8 days after infarction. They had been trained to stand unsedated in a sling. Bipolar electrograms (30 to 500 Hz, 1 mV/cm) were recorded from the left atrial appendage and noninfarcted area of the left ventricle except when the electrodes were being used for stimulation. The subcutaneous electrocardiographic signal (direct current to 500 Hz, 1 mV/cm) corresponded to an orthogonal Z lead. After each animal had settled in the sling, resting sinus cycle length was recorded.

Pacing protocol for induction of tachycardia. Pacing was performed with a Medtronic programmable constant-current stimulator with the use of square-wave stimuli of 2 msec duration at 3 times diastolic threshold. The stimulation protocol was as follows: (1) Atrial pacing frequency series at cycle lengths of 400 to 160 msec. (2) Premature ventricular stimulation with single (V2) and double (V2V3) extrastimuli after every 8 ventricular paced beats at basic cycle lengths of 350, 300, and 250 msec. The effective refractory period to single ventricular extrastimuli (VERP) was measured during ventricular drive pacing at a cycle length of 300 msec. (3) Ventricular pacing fre-
frequency series at cycle lengths of 400 to 160 msec. (4) Bursts of four to five ventricular extrastimuli at cycle lengths of 200 to 130 msec, with 10 attempts at each cycle length. Bursts were not synchronized to the R wave.

The pacing protocol was performed in an identical manner on each day of the study. The end point of the stimulation on each occasion was development of sustained ventricular tachycardia or ventricular fibrillation, or completion of the full pacing protocol. Unless cardioversion had been necessary, the reproducibility of induction of each tachycardia was confirmed three times.

Sustained ventricular tachycardia was defined as a stable tachycardia with a uniform QRS pattern that required termination by overdrive pacing or, if necessary, by cardioversion. Nonsustained ventricular tachycardia was defined as any self-terminating response of 4 or more pleomorphic ventricular beats.

**Repeat study.** At the end of each programmed stimulation series, the dogs were returned to the animal quarters. Programmed ventricular stimulation to the same end point was repeated on a daily basis until day 7 or 8.

**Statistical methods.** Results are expressed as mean ± SD. Differences between groups were assessed by Student’s t test. Two-tailed p values <.05 were considered indicative of a significant difference.

**Results**

**Ventricular tachyarrhythmias.** A total of 57 programmed stimulations was performed (mean 3.8 per dog). Stimulation produced ventricular fibrillation in four (7%), sustained ventricular tachycardia in 18 (32%), nonsustained ventricular tachycardia in 28 (49%), and no ventricular tachycardia in seven (12%) studies. A sustained tachyarrhythmia (tachycardia or fibrillation) was produced on one or more occasions in 11 of 15 dogs (73%), and at least nonsustained ventricular tachycardia was produced in each dog.

Ventricular fibrillation occurred immediately after stimulation in two cases, accompanied by appearance of continuous chaotic electrical activity in the surface electrocardiogram and ventricular electrogram. In two other cases 7 to 12 beats of rapid polymorphic ventricular tachycardia, cycle lengths 116 and 155 msec, were noted before the onset of ventricular fibrillation. In two other cases rapid but monomorphic ventricular tachycardia (cycle lengths 119 and 121 msec) degenerated to ventricular fibrillation after 15 to 30 sec; these two were considered examples of secondary fibrillation. Excluding these two instances the mean cycle length of stable sustained ventricular tachycardia was 188 ± 27 msec. The mean number of unstimulated beats during nonsustained ventricular tachycardia was 8.1 ± 7.2, with a cycle length of 142 ± 7 msec. This cycle length was significantly shorter than that recorded during stable sustained ventricular tachycardia (p < .001).

**Daily variation in results of programmed stimulation.** The results of the first programmed stimulation study on day 3 were used to divide the dogs into two groups according to whether a sustained tachyarrhythmia was induced or not. Group 1 comprised two dogs with primary ventricular fibrillation and four with stable monomorphic ventricular tachycardia. Of the nine dogs in group 2, eight had nonsustained ventricular tachycardia and in one no tachycardia was induced. The results of programmed stimulation in dogs in groups 1 and 2 on subsequent days are shown in figures 1 and 2.

The two dogs that showed primary ventricular fibrillation on day 3 could not be resuscitated. Of the four that had stable sustained ventricular tachycardia on day 3, two developed ventricular fibrillation on day 4. One dog was successfully defibrillated and produced no further sustained tachycardias on subsequent testing. Two dogs had stable sustained ventricular tachycardia on 4 consecutive days, although the cycle length varied on a day-to-day basis from 185 to 235 msec in one and from 169 to 203 msec in the other. One dog died on day 6 as a result of ventricular fibrillation produced by overpacing in an attempt to end the tachycardia, while the other dog showed no further sustained arrhythmias on days 7 and 8. Figure 2 shows the results of the daily stimulation in group 2. Of eight dogs with nonsustained ventricular tachycardia on day 3, five had developed sustained tachycardia by day 6 or 7.

**Mode of initiation of tachyarrhythmias.** No tachyarrhythmias were induced by rapid atrial pacing. Ventricular fibrillation was induced by double ventricular

![FIGURE 1. Result of programmed stimulation in six dogs that developed ventricular fibrillation or sustained ventricular tachycardia on day 3. Of the four dogs that showed sustained ventricular tachycardia, two developed ventricular fibrillation on day 4 and two had stable sustained ventricular tachycardia on 4 consecutive days. Two dogs eventually became "stable"; no sustained tachyarrhythmia was inducible. Each symbol represents one programmed stimulation. Episodes of use of direct-current shock in an attempt to terminate arrhythmias are represented as follows: ▲ = successful cardioversion/defibrillation; * = unsuccessful defibrillation.](http://circ.ahajournals.org/)

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FIGURE 2. Results in nine dogs that did not show ventricular fibrillation or sustained ventricular tachycardia on day 3. By day 6 or 7, five of the nine had progressed from nonsustained to sustained ventricular tachycardia. Each symbol represents one programmed stimulation. Symbols are as in figure 1.

premature stimuli ($V_1V_2V_3$) in one instance, and by ventricular burst pacing in three. Sustained monomorphic ventricular tachycardia was induced by $V_1V_2$ stimulation in three studies (17%), by $V_1V_2V_3$ in three studies (17%), and by ventricular burst pacing in 12 studies (67%). Nonsustained ventricular tachycardia was induced by $V_1V_2$ stimulation in four experiments (14%), by $V_1V_2V_3$ in 20 (71%), and burst pacing in four (41%). No consistent pattern of change in the mode of induction of tachycardia from day to day was noted.

VERP. Diastolic pacing thresholds varied from 1 to 3 mA during the study, with no discernable consistent trend. Mean VERP for all dogs was $148 \pm 13$ msec on day 3, and fell to $121 \pm 9$ msec on day 6 ($p < .001$). Mean VERP in the six dogs that had sustained ventricular tachycardia or fibrillation on day 3 was $154 \pm 12$ msec, compared with $144 \pm 13$ msec in the nine others (NS). There was a general trend towards shortening of VERP with time, irrespective of the outcome of programmed stimulation (figure 3).

Sinus cycle length (SCL). Mean SCL in all dogs was $414 \pm 55$ msec on day 3 and $376 \pm 38$ msec on day 6 (NS). There was no significant difference between SCL in the group 1 dogs and that in the others ($441 \pm 46$ vs $397 \pm 55$ msec). The mean SCL in the five dogs in group 2 that progressed from nonsustained to sustained ventricular tachycardia during the study was $404 \pm 18$ msec on day 3 and $401 \pm 41$ msec on the day of onset of sustained tachycardia.

Discussion

Our results demonstrate a considerable daily variation in the inducibility of ventricular tachyarrhythmias in the early postinfarction period. We used a pacing protocol that was similar to that in previous studies of chronic canine infarction. Although double extrastimuli may produce ventricular fibrillation in the noninfarcted heart under open-chest conditions, there is a low incidence of false-positive induction of fibrillation, and none of sustained ventricular tachycardia, in conscious closed-chest dogs. The variation in inducibility of ventricular tachyarrhythmias after experimental myocardial infarction has received little attention, since most groups have used anesthetized open-chest dogs in which serial studies were impracticable.

Karagueuzian et al. studied induction of ventricular tachycardia in conscious dogs 2 to 9 days after infarction. Only two of 10 dogs that underwent permanent left anterior descending occlusion developed sustained ventricular tachycardia, each of these on one occasion only. Sustained ventricular tachycardia was induced on day 3 in 11 of 16 dogs that had undergone occlusion and reperfusion. Of the dogs showing sustained ventricular tachycardia on day 3, none had in-

FIGURE 3. Changes in VERP over time in dogs of group 1 (top) and group 2 (bottom). There was a trend toward shortening of VERP with time in most dogs, irrespective of the outcome of programmed stimulation. Symbols designate outcome of programmed stimulation as follows: * = ventricular fibrillation; = sustained ventricular tachycardia; = nonsustained ventricular tachycardia; = no ventricular tachycardia; ? = VERP inadvertently not recorded.
ducible sustained or nonsustained ventricular tachycardia by day 6, and no dog progressed from nonsustained to sustained ventricular tachycardia as they did in our study. Some major differences between the study of Karagueuzian et al. and the present work must be pointed out. The previous investigators used an occlusion/reperfusion preparation that produces a heterogeneous area of infarction unlike the uniform infarct produced by permanent occlusion, and they did not use methylprednisolone, which has been shown empirically to favor ventricular tachycardia induction. We used a pacing protocol involving $V_1 V_2 V_3$ and burst pacing, while Karagueuzian et al. used only $V_1 V_2$ stimulation.

In a later study of conscious dogs subject to the same occlusion/reperfusion protocol, the same group showed that $V_1 V_2$ stimulation on days 3 to 5 produced sustained ventricular tachycardia in 14% of dogs, and ventricular burst pacing produced tachycardia in 26%, giving an overall incidence of 29%. Our success rate for induction of sustained tachyarrhythmias (ventricular tachycardia and ventricular fibrillation) was 22 of 57 studies (39%) in 11 of 15 dogs (73%).

Echt et al. reported a study of multiple programmed ventricular stimulation performed once or twice weekly in 13 dogs that had undergone 2 hr occlusion and reperfusion of the left anterior descending artery. Sustained ventricular tachycardia, defined as a cycle length greater than 180 msec, occurred in only two of 178 programmed stimulation studies, with ventricular flutter in 25, primary ventricular fibrillation in 128, and flutter degenerating into fibrillation in 23. A number of dogs finally underwent open-chest electrophysiologic study, but the results were not significantly different from those in the closed-chest conscious preparation. The high incidence of ventricular fibrillation in their study may be the result of the use of triple extrastimuli. We did not use this technique, and were not able to continue our study beyond day 8, so we cannot comment on the late changes in inducibility of ventricular tachycardia in our preparation. There are differences in cellular electrophysiologic properties between the time periods of 3 to 5 days and 8 to 15 days after infarction, with recovery of membrane potential, action potential amplitude, and rate of phase O depolarization. Thus, the early postinfarction period is one of changing electrophysiologic properties, although cellular electrophysiologic abnormalities are still demonstrable weeks to months after infarction in both experimental animals and man.

Our study was of course confined to induced rather than spontaneous tachyarrhythmias. We used implanted stimulating electrodes to provide a consistent site for stimulation, and did not observe major changes in stimulation threshold. We were, however, unable to investigate multiple sites of stimulation, particularly at the border of the infarcted area, where the inducibility of ventricular tachycardia may vary considerably.

The ability to induce a sustained tachyarrhythmia may depend critically on the invasion of an area of potential reentrant activity by a sufficiently premature stimulus. It was therefore of interest to note that the mean VERP was not significantly different in the dogs that developed sustained ventricular tachycardia or fibrillation on day 3 than in the others. The values for VERP at a cycle length of 300 msec were similar to those previously reported. Unlike Karagueuzian et al., we observed a general trend toward shortening of VERP with time. However, this did not appear to be a critical factor in the inducibility of sustained ventricular tachyarrhythmias at any stage. One possible explanation for the shortening of VERP with time might be an increase in sympathetic tone. This might have occurred as a result of psychological stress, which is known to reduce the threshold for repetitive ventricular responses. We did not measure plasma catecholamine levels, but we also did not observe a significant increase in basal heart rate during the study, despite the decreases in VERP. Furthermore, shortening of VERP did not occur only in dogs that had experienced sustained ventricular tachycardia or cardioversion. On the basis of this indirect evidence, at least, there appeared to have been no major change in sympathetic activity.

In conclusion, we have shown in this experimental study that there is considerable day-to-day variation in the inducibility of sustained ventricular tachyarrhythmias in the early postinfarction period. Similar variation in inducibility of tachyarrhythmias may occur in the early postinfarction period in man, and may be of relevance to the optimal timing of electrophysiologic studies for prognostic evaluation.

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