Ventricular Electrical Instability in the Conscious Dog

Effects of Psychologic Stress and Beta Adrenergic Blockade

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The effect of psychologic stress on cardiac vulnerability was examined in 10 conscious dogs. The repetitive extrasystole threshold was employed as a measure of susceptibility to ventricular fibrillation. Instrumental aversive conditioning constituted a stressful environment. The repetitive extrasystole threshold decreased by nearly 50 percent during 3 days in which the animals were exposed to the stressful environment. When Tolamolol hydrochloride, a cardioselective beta adrenoceptor blocking agent, was administered before a stress session, the repetitive extrasystole threshold was unaltered from the control value. Thus, stress-evoked changes in cardiac vulnerability are mediated through the sympathetic nervous system.

The role of psychologic stress in predisposing to cardiac arrhythmias is well recognized clinically. However, precise data documenting this relation have been difficult to obtain in man or in the animal laboratory. With growing interest in the problem of sudden death due to ventricular fibrillation, attention has been devoted to alterations in ventricular vulnerability during various stressful states. Recently it has been demonstrated in dogs that the threshold of the ventricular vulnerable period for eliciting repetitive extrasystoles is significantly lower in an aversive than in a placid environment.[1] It has also been found that animals placed in stressful restraint after myocardial infarction experience ventricular arrhythmias, including ventricular tachycardia.[2] In pigs protected against psychologic stress, the onset of ventricular fibrillation after coronary arterial ligation is either retarded or entirely prevented.[3] Moreover, pharmacologically restrained pigs subjected to electrical stimulation undergo severe acute cardiomyopathy and 13 percent die suddenly.[4]

This study was undertaken to evaluate the effects of psychologic stress upon ventricular electrical stability in the conscious dog. The assumption entertained was that a change in cardiac electrical stability was associated with increased susceptibility to ventricular fibrillation.[5] The underlying hypothesis was that a psychologically stressful environment would increase cardiac electrical instability. Instrumental aversive conditioning was the experimental paradigm employed to produce psychologic stress.[6–8] Since certain types of stressors in man affect cardiac function through sympathetic nervous mediation,[9] these studies were performed with and without blockade of beta adrenergic activity. Cardiac electrical stability was determined by measuring the threshold current necessary to provoke repetitive ventricular extrasystoles. It has been demonstrated that the repetitive extrasystole threshold can be used as a precise measure of the vulnerable period threshold for ventricular fibrillation.[1,10]

Methods

Ten mongrel dogs, weighing 8.5 to 17 kg, were anesthetized with intravenously administered sodium pentobarbital, 32.5 mg/kg body weight. Two bipolar cardiac

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catheters were positioned under fluoroscopic control by way of a jugular vein. One catheter (Medtronics no. 5819 platinum electrodes with an interelectrode distance of 1.5 cm and pole width of 3 mm) was placed at the right ventricular apex and was used for ventricular pacing; a second catheter (made from two Alpha no. 28 7/36 polyvinyl chloride wires), 2 cm proximal to the first, was used to obtain an artifact-free electrocardiographic signal. The catheters were passed subcutaneously and were externalized at the nape of the neck, where elastic bandages held them securely in place. The animals were allowed 1 to 3 days to recover. Rectal temperature was monitored daily. If at any time during the course of these experiments the temperature exceeded 39.9°C, the animal was temporarily removed from the study and treated with antibiotic agents.

After recovery, the animals were adapted to the instrumental conditioning apparatus for 30 minutes daily on 2 consecutive days. The apparatus consisted of a flexible counterbalanced restraint harness suspended in a ventilated cage.[11] The dog was strapped into the harness and was allowed movement up and down as well as forward and backward but was prevented from turning around. The implanted catheters were connected with cables to an oscilloscope and pen write-out for electrocardiographic visualization and to a Tektronix pacing system for ventricular pacing conducted in an adjoining room.

Protocol: After adaptation, the animals were studied for 4 consecutive days. On each day, a control period of approximately 30 minutes was followed by a stress period of approximately 20 minutes. The onset of the stress period was signaled by a 6 v red light positioned on the front wall of the conditioning cage as well as by white noise, a signal with a flat energy spectrum containing both high and low frequency components. The behavioral stress required the animal to learn to avoid a programmed electric shock (instrumental avoidance conditioning). Shock electrodes were secured on the shaved surface of the left hind limb. At the onset of the stress period a 1 kilohertz tone sounded. This was followed, 10 seconds later, by an inescapable 3 milliampere alternating current shock of 1 second's duration. After shock, the tone went off and remained off for 10 seconds. The sequence of tone and shock was repeated two additional times. Thereafter, the animal's response could terminate the tone and avoid the shock. The appropriate response consisted of an approach to a panel on the front of the cage. Initially, any forward movement resulted in shock avoidance. Later, effective avoidance required the animal to make a distinct approach toward the panel. The intensity of the shock was increased if the animal showed no approach response at the onset of the tone. The presentation of tones and shocks was programmed with use of specially designed integrated circuits.

Repetitive extrasystole threshold: This threshold was determined as a measure of cardiac electrical stability and the susceptibility to ventricular fibrillation.[1,10] Electrical testing of the heart was accomplished using a special purpose stimulator (designed by Robert Cannon). This instrument was provided with a fixed rate pacemaker with appropriate circuitry to inhibit pacemaker discharge during ventricular stimulation. Cardiac testing was performed by delivering sequences of three square wave constant current cathodal pulses of 2 msec duration, with a variable amplitude of 0 to 100 milliamperes (ma) accuracy ±3 percent (standard error) and timing accuracy ±3 msec. The first pulse was electrically timed from the R wave of the preceding paced beat. Electrical testing was conducted according to the technique designated as sequential R/T pacing.[12] This technique was employed for determining the repetitive extrasystole threshold.

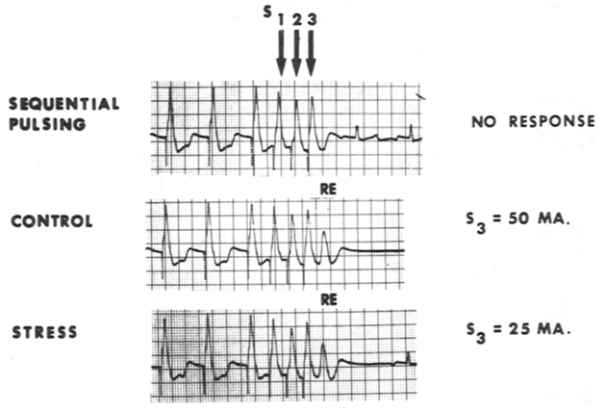

FIGURE 1. Sequential pulsing in the conscious dog. In the **top panel,** three pulses, S_1, S_2 and S_3, are sequentially discharged after a basic paced beat. No repetitive response occurs. Under control conditions **(center panel)** an S_3 current of 50 ma is necessary to elicit a repetitive extrasystole, labeled RE. In the stress paradigm **(bottom panel)** an S_3 current of only 25 ma provokes a repetitive extrasystole.

Two determinations of the repetitive extrasystole threshold were made daily, once before and once during the stress session. The procedure for each determination was as follows:

1. The pacing threshold was determined, and pacing was maintained throughout testing at a rate of 200 beats/min with a current at twice threshold level.
2. The diastolic threshold to a 2 ma pulse (S_1) delivered after a basic paced beat was determined. The current was then set at twice threshold and the effective refractory period was obtained. The effective refractory period was defined as the minimal interval from the preceding paced beat at which S_1 first resulted in a ventricular response in two of three determinations.
3. The diastolic threshold and effective refractory period for a second (S_2) and third (S_3) sequential pulse were likewise determined.
4. The vulnerable period of S_3 was scanned in 1 msec decrements beginning 10 msec beyond the twice threshold effective refractory period and terminating at the refractory period border with successively higher current pulses. To reduce the probability of accidental ventricular fibrillation, vulnerable period scans were made in 2 ma increments up to 10 ma, and in 5 ma increments thereafter.

In no case were currents greater than 80 ma applied. The repetitive extrasystole threshold was defined as the minimal current that resulted in a repetitive extrasystole in two of three determinations. Figure 1 demonstrates such a repetitive extrasystole obtained before and during stress. If at any time the repetitive extrasystole threshold was obtained with twice threshold values during the control period, the third pulse (S_3) was not used, so that the vulnerable period of S_2 was scanned instead for both control and stress periods. If the repetitive extrasystole threshold was not obtained during testing, then 80 ma was chosen as the repetitive extrasystole threshold for statistical purposes.

Beta adrenergic blockade: On day 3, all animals received the $beta_1$ cardiospecific drug, Tolamolol®* (1-{2-[4-carbamoylphenoxyl]ethylanimo}-3-[2-methylphenoxy] propan-2-ol hydrochloride).[13-15] This beta adrenergic blocking drug was given intravenously in a dose of 4 mg/kg immediately before

* Tolamolol® was made available by Dr. Colin R. Taylor from Pfizer Central Research, Groton, Conn.

the control repetitive extrasystole threshold determination. The heart rate response to isoproterenol (0.4 mg/kg intravenously) was obtained during the control period before administration of Tolamolol and again after the repetitive extrasystole threshold determination during stress. On days 1, 2 and 4, repetitive extrasystole thresholds were examined without drug intervention.

Statistical analysis: The repetitive extrasystole threshold and heart rate data were analyzed with "within subjects" analyses of variance[16]; in this design, each animal receives every treatment combination. Thus all animals were studied for 4 days and repetitive extrasystole thresholds and heart rates were determined twice each day in each animal. Follow-up analyses on these data were performed using critical difference t tests.[16] Finally, changes in effective refractory period were analyzed with sign-rank tests.[17]

Results

Stress caused a significant reduction in the repetitive extrasystole threshold in each of the 10 dogs tested. The repetitive extrasystole thresholds for the control and stress periods are presented for days 1 to 4 in Figure 2. On the 3 days without administration of the beta adrenergic blocking drug, the mean decrease in threshold was 49.5 percent (P <0.01). Analysis of variance revealed an overall effect of days (P <0.05), of control versus stress (P <0.001) and of their interaction (P <0.001). These reductions were nearly the same during stress on days 1, 2 and 4 and amounted to alterations from control values of 44.7, 52.2 and 51.5 percent, respectively. These values are not significantly different from each other. The mean decrease in current was from 42.8 to 21.7 ma.

On day 3, when Tolamolol was administered before the stress session, the repetitive extrasystole threshold did not decrease. Thus, the control value was 42.0 ± 5.5 ma (standard error) and during the stress period the threshold for a repetitive response was 44.5 ± 5.7 ma. In fact, a slight but nonsignificant increase (6.0 percent) in the repetitive extrasystole threshold was observed.

The effective refractory period data were analyzed by examining the change scores for S_1, S_2 and S_3 from daily control values. The mean effective refractory period change scores for S_1, S_2 and S_3 were combined on days 1 through 4 and are depicted in Figure 3. Sign-rank tests for paired observations revealed significant decreases in the effective refractory period on days 1, 2 and 4 (P <0.05), but not while the animals received Tolamolol on day 3.

The effectiveness of beta adrenergic blockade was assessed by measuring the heart rate response to isoproterenol before and after beta blockade. These results are depicted in Figure 4. Analysis of variance revealed a significant effect of Tolamolol (P <0.001). Critical difference t tests (P <0.01) demonstrated that Tolamolol reduced significantly the acceleration in heart rate resulting from the intravenous injection of isoproterenol (from a mean increase of 135 to an increase of 21 beats/min).

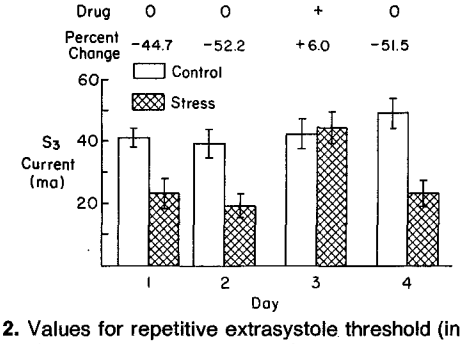

FIGURE 2. Values for repetitive extrasystole threshold (in ma) for 4 consecutive days of stress testing (mean ± standard error of the mean). In each of 3 days without Tolamolol, stress caused a significant lowering of the threshold. The plus sign (+) indicates the day on which beta blockade was administered. Figures represent the percent change in S_3 threshold from the control value on the day of the testing.

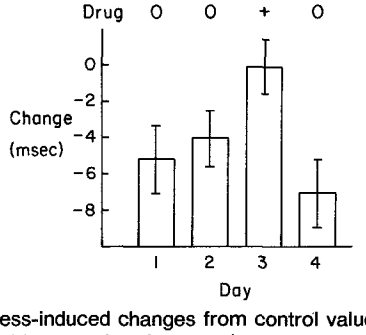

FIGURE 3. Stress-induced changes from control values in effective refractory period (mean values in msec ± standard error of the mean). Negative values denote recession of the effective refractory period earlier into electrical diastole. The plus sign (+) indicates the day on which beta adrenergic blockade with Tolamolol was administered.

Discussion

Role of neural mechanisms in genesis of cardiac arrhythmias: For nearly 2 centuries psychologic factors have been implicated in the provocation of sudden death in man.[18–26] To date, the data documenting a causal role for higher nervous activity is at best cir-

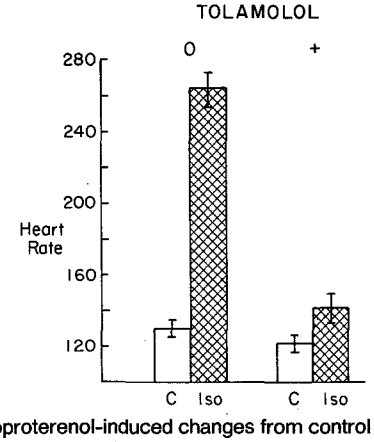

FIGURE 4. Isoproterenol-induced changes from control values in heart rate with (+) and without (0) beta adrenergic blockade with Tolamolol (mean values in beats/min ± standard error of the mean). C = control; Iso = isoproterenol.

cumstantial.[26,27] However, there is a substantial body of evidence demonstrating the role of neural mechanisms in the genesis of cardiac arrhythmias. In experimental animals, midbrain stimulation has evoked diverse arrhythmias including ventricular fibrillation.[28–30] Hypothalamic stimulation resulted in a 10-fold greater incidence of ventricular fibrillation in dogs with acute occlusion of the left anterior descending coronary artery than in the unstimulated animal.[31] It has also been demonstrated that electrical stimulation of the cardioaccelerator center in the midbrain significantly lowers the vulnerable period threshold for ventricular fibrillation.[32]

Arrhythmias have also been elicited by activation of the peripheral sympathoadrenal system. Han et al.[33] found a marked reduction in threshold for multiple ventricular extrasystoles during stellate ganglion stimulation. Verrier et al.[34] demonstrated that the predisposition to ventricular fibrillation ensuing from sympathetic nervous stimulation was unaffected by preventing concomitant increases in heart rate and blood pressure but was annulled by pretreatment with reserpine. Schaal et al.[35] reported that total cardiac denervation prevented ventricular tachycardia in 8 of 10 awake dogs after coronary arterial ligation. As early as 1931, Leriche et al.[36] found that survival rates after coronary occlusion increased in dogs when the animals had prior cardiac sympathectomy.

Repetitive extrasystole threshold as a measure of vulnerability to ventricular fibrillation: None of the studies cited examined the possible role of psychologic factors in altering cardiac susceptibility to ventricular fibrillation. Assessing the ventricular vulnerable period threshold for ventricular fibrillation in the conscious animal has many methodologic difficulties. The need to use painful stimuli of high current content, the use of ventricular fibrillation as an end point and the necessarily traumatic resuscitative procedures, all prevent adequate examination of the role of psychologic variables. It has recently been demonstrated that a repetitive extrasystole can be elicited consistently at 66 percent of the current required for provoking ventricular fibrillation when a single stimulus is discharged in the vulnerable period of the cardiac cycle.[10] The nadir of the zone for the repetitive extrasystole coincides with that for induction of ventricular fibrillation. Furthermore, the shift in these threshold nadirs are synchronous during stellate ganglion or vagal nervous stimulation and during beta adrenergic blockade. Consequently, the repetitive extrasystole threshold can be used as a surrogate ventricular fibrillation threshold, subject to the same electrophysiologic considerations as that threshold.[10] Thus a means is provided for studying changes in cardiac vulnerability without provoking ventricular fibrillation.

To diminish the current for eliciting a repetitive extrasystole, triple pulsing has been employed. Thompson and Lown[12] have noted that when three such sequential R/T pulses are delivered early in diastole, the current requirement for inducing ventricular fibrillation is reduced. In the animal with acute myocardial ischemia the current level of the third pulse necessary to provoke ventricular fibrillation is drastically lowered to near threshold level for inducing a propagated ventricular response during diastole.[37] By employing the technique of R/T pulsing and having as an end point the repetitive extrasystole, it is possible to study the unrestrained conscious animal.[1]

Psychologic stress and susceptibility to ventricular fibrillation: It has previously been demonstrated that psychologic stress can lower the repetitive extrasystole threshold. Thus, when comparing a tranquil cage environment with a stressful environment in which dogs were restrained and given an unavoidable single shock, animals in the latter environment had a 67 percent decrease in the repetitive extrasystole threshold.[1] In the present study, threshold measured in the same environment before and during stress was decreased 50 percent during stress. This slightly smaller decrease may be related to psychologic provocation caused by the test environment. Thus, the animals in this study may already have experienced some stress and consequent reduction in the repetitive extrasystole threshold during the control period, as suggested by their tachycardia (mean heart rate 130 beats/min). By contrast, in the earlier cage-sling experiment, the mean heart rate was 100 beats/min while the animal was in the tranquil environment. In both experimental studies there was a substantial reduction in the repetitive extrasystole threshold with psychologic stress. This finding indicates that an aversive environment significantly enhances the suspectibility of the dog's heart to ventricular fibrillation.

Effect of beta adrenergic blockade: It has been assumed that the lowering in the repetitive extrasystole threshold is related to enhanced sympathetic discharge occasioned by the instrumental aversive conditioning. This assumption is supported by events on days 3 and 4: When the animal received Tolamolol hydrochloride, the change in repetitive extrasystole threshold resulting from stress was abolished, only to be demonstrated again when no drug was administered. Because the Tolamolol simultaneously nearly completely attenuated the isoproterenol-induced tachycardia, it is reasonable to ascribe the prevention of reduction in repetitive extrasystole threshold to the beta adrenergic blocking action of this drug. Nevertheless, a direct electrophysiologic and antifibrillatory effect cannot be ruled out because Tolamolol has been reported to prolong the functional refractory period and raise the ventricular fibrillation threshold in open chest anesthetized dogs.[38] However, because the open chest animal preparation may have increased sympathetic tone,[39] the effect of Tolamolol on the ventricular fibrillation threshold might be attributed as well to its beta adrenergic blocking action on such sympathetic discharge. The weight of evidence indicates that the shortening of the duration of the refractory period as well as the reduction in the repetitive extrasystole threshold are mediated by the sympathetic nervous system.

Clinical implications: If the occurrence of ventricular fibrillation and sudden death in man is related to

neural input by way of the sympathetic nervous system, beta adrenergic blocking agents may prove of prophylactic value. The mechanism for such salutary action would derive from the prevention of the reduction in ventricular fibrillation threshold that attends increased sympathetic nervous traffic to the heart. Recent clinical findings are relevant in this context. Three studies[40–42] have now been reported in which beta adrenoceptor antagonists were given for long periods in patients who had recovered from acute myocardial infarction. In each study a statistically significant reduction in sudden death was observed.

It must be noted that changes in repetitive extrasystole threshold relate to a possible susceptibility to ventricular fibrillation and not to the occurrence of ventricular extrasystoles. To date, we know of no data that clearly formulate a relation between cardiac vulnerability and the presence of ventricular ectopy in man. The data in our study do not allow such a formulation.

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