Sudden Cardiac Death — 1978

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SUMMARY   With the development of coronary care units in the 1960s, attitudes toward sudden cardiac death (SCD) began to change as physicians learned that cardiac arrest was reversible. The problem of SCD has two aspects — an acute, precipitating factor and a chronic predisposition to electrical instability of the myocardium. Resolution of the problem requires identification and protection of the potential victim. Ventricular premature complexes (VPCs) have been related to the development of serious arrhythmias and early death, but the mere presence of VPCs does not discriminate risk of subsequent fatality. VPCs should be graded according to frequency, persistence, multiformity, repetitive pattern and degree of prematurity. Provocation of repetitive extrasystoles by R-on-T pacing may indicate the presence of a reduced threshold for ventricular fibrillation (VF). Prophylactic antiarrhythmic therapy may help protect patients resuscitated from VF against recurrent cardiac arrest. Neuropharmacologic factors perhaps affecting central nervous system sympathetic activity can alter cardiac vulnerability and may protect against VF. Findings in dogs indicate that psychologic stress can reduce the cardiac threshold for VF. If psychologic factors predispose to ventricular arrhythmias by increasing the level of sympathetic tone, lessening neural sympathetic activity should reduce the incidence of SCD.

SUDDEN CARDIAC DEATH (SCD) is one of the major challenges to contemporary cardiology. Its sheer magnitude demands attention, claiming over 400 thousand lives annually, or about 60% of all coronary heart disease fatalities. The problem of sudden death has been recognized since the beginning of recorded history, yet before the 1960s, SCD received scant attention from clinical and research communities. In part this related to the prevailing perception that SCD was the ultimate expression of severe, far-advanced and irreversible coronary atherosclerosis. Since the SCD was unexpected and struck down the seemingly healthy subject outside the hospital, the physician deemed it an act of fate before which he or she was largely helpless.

As is often true in science, new methodologies not only usher in new content, but also mold new attitudes. In the case of SCD it was the burgeoning coronary care units (CCU) of the 1960s that stimulated a new direction. CCU experience largely dispelled the sense of futility, for it became rapidly evident that cardiac arrest was reversible. Patients promptly resuscitated from primary electrical failure consistently recovered and survived for variable and prolonged periods determined by the extent of their underlying heart disease. Because ventricular fibrillation (VF) had its highest incidence at the beginning of a myocardial ischemic episode, it was logical to assume that this same mechanism accounted for out-of-hospital sudden death.

The CCU demonstrated that VF can be reversed as well as prevented. These findings have led to the development of two distinct strategies:[1] 1) to reach the patient promptly and initiate effective cardiopulmonary resuscitation,[2] and 2) to identify the patient at increased risk for SCD and institute a prophylactic program against potentially fatal ventricular arrhythmias.[3]

Community Response to Cardiac Arrest

The logic of a well-organized community program permitting immediate response to out-of-hospital cardiac arrest is not debatable. The critical factor is the expeditious reaching of the victim by personnel fully tutored in basic life support. This necessarily requires that large sectors of the population be trained and their skill in cardiopulmonary resuscitation be finely honed at all times for the unexpected emergency. In Seattle, where such a program has been in operation for over 6 years, there have been 346 long-term survivors out of 1710 episodes of VF encountered in the community.[4] The percentage of immediate resuscitations has improved annually, as has the yield in long-term survivors. A disquieting aspect of the Seattle experience is the high incidence of recurrent cardiac arrest. The mortality rate has been 26% at 1 year and 36% at two years. The problem of SCD has two aspects — an acute, precipitating trigger as well as a chronic predisposition to electrical instability of the myocardium. The mere reversal of the cardiac arrest does not obviate the underlying electrophysiologic abnormality. For those successfully resuscitated there can be no assurance that the good fortune of a prompt response by a trained medical team will be repeated. Resolution of the problem of SCD ultimately requires identification and protection of the potential victim.

Detecting the Patient at Risk

The essential strategy currently followed in identifying the patient at risk and in preventing VF relies on the hypothesis that the ventricular premature complex (VPC) constitutes a risk factor.[1, 3] Two questions, therefore, must be answered: 1) What is the evidence that VPCs indeed indicate predisposition to sudden death? 2) Is there any basis for concluding that control of VPCs will protect against VF?

Experience with patients who have an acute myocardial infarction in the CCU has shown the important relationship of VPCs to the development of more serious cardiac arrhythmias and early death.[5-7] The significance of VPCs occurring in coronary patients at times other than during the acute episode requires separate consideration. Recent reports have associated VPCs with an increased risk of out-of-hospital cardiac death.[8-16] However, when longer periods of ambulatory monitoring are done, nearly 90% of patients with coronary heart disease exhibit ectopic activity.[17, 18] Thus, the mere presence of VPCs cannot be a significant prognostic discriminator of risk for subsequent fatality. It has been our view that VPCs need to be graded according to certain attributes of frequency, persistence, multiformity, repetitive pattern and degree of prematurity[3, 18] (table 1). Only frequent advanced grades or complex forms of VPCs impart enhanced risk for future SCD in patients with coronary heart disease. This thesis has now been corroborated in the Health Insurance Plan of New York prospective epidemiologic studies.[19] From a male population of 120,000 aged 35–74 years, 1739 with prior myocardial infarction were monitored for 1 hour at a standard baseline examination and were followed for mortality for an average period of 24.4 months. The presence of complex VPCs (R-on-T, runs of two or more, multiform or bigeminal) in the monitoring hour was associated with a risk of SCD three times that of the men free of such arrhythmia. The VPCs made an independent contribution to increased risk of fatality that persisted throughout the observation period.

Inadequacies of VPCs as Risk Indicators for SCD

We do not know whether the VPC represents the trigger for repetitive activity leading to VF or is merely an innocuous concomitant in the electrically unstable heart. In the former case, its suppression might prove protective; in the latter, the underlying electrophysiologic derangement may continue, even though ectopic activity is controlled. In animal experiments, a dissociation between the presence of VPCs and predisposition to VF can be shown. Thus, when dogs are pretreated with antiarrhythmic drugs and then subjected to acute coronary artery occlusion, they are protected against VF, though no substantial reduction may be observed in either the frequency or the grade of ectopic activity (fig. 1). The clinician also confronts the problem that in using the VPC as a marker of enhanced risk for SCD, there is no certainty as to the extent of ectopic activity suppression necessary to provide adequate prophylaxis. This issue is further complicated by the random occurrence and low reproducibility of advanced grades of VPCs. In 65 patients with angiographically proved coronary disease and VPCs on 24-hour monitoring, repetitive arrhythmias were reproducible in only 40% of patients[19] (fig. 2). The need is urgent for more direct indicators of the electrophysiologic lesions that predispose the myocardium to VF.

TABLE 1. *A Grading System for Ventricular Premature Complexes (VPCs)*

Grade	VPC Characteristics
0	No ventricular beats
1A	Occasional, isolated VPCs ($< 30/hr$) $< 1/min$
1B	Occasional, isolated VPCs ($< 30/hr$) $> 1/min$
2	Frequent VPCs ($> 30/hr$)
3	Multiform VPCs
4A	Repetitive VPCs; couplets
4B	Repetitive VPCs; salvos
5	Early VPCs (i.e., abutting or interrupting the T wave)

Sample equation

$$0^3 \quad 1A^0 \quad 1B^4 \quad 2^6_{760} \quad 3^6_2 \quad 4A^2_3 \quad 4B^2_{4-7} \quad 5^1_3$$

Grade	Explanation
0	Occurred during 3 hours
1A	No infrequent VPCs
1B	Infrequent VPCs but greater than $1/min$ observed during 4 hours
2	Occurred during 6 hours (with a total of 760 VPCs)
3	Occurred during 6 hours and exhibited two forms
4A	Occurred during 2 hours and their greatest frequency in any 1 hour was three
4B	Occurred during 2 hours; there were four paroxysms; the longest duration was seven cycles
5	An early VPC was observed three times during a single hour in the 24-hour monitoring session

This grading system is applied to a 24-hour monitoring period and indicates the number of hours within that period that a patient has VPCs of a particular grade, which is expressed in the resulting "equation" as a superscript. Subscripts are used to indicate particular aspects of the VPCs of a given grade. In the sample equation, for example, the subscript for grade 2 indicates the approximate total number of grade 2 VPCs over the 24-hour period; for grade 3 it denotes the number of different forms observed in any single hour; for grade 4B the two subscripts indicate first the largest number of paroxysms of tachycardia in a single hour and the second denotes the maximum number of successive cycles; for grade 5 the subscript represents the largest number of early ectopic beats in any single hour.

Other Markers of Cardiac Vulnerability

How can the presence of electrical instability be directly demonstrated? In the normal and the diseased heart, a single electrical stimulus causes but a single response. However, markedly suprathreshold stimuli discharged during the vulnerable period of the cardiac cycle induce repetitive responses and VF. Even in the presence of acute myocardial ischemia, suprathreshold discharges are required to evoke VF. A critically important question is whether near-threshold currents, just sufficient for eliciting a propagated response in diastole, can induce repetitive electrical activity. We have found in the animal with acute coronary artery occlusion that when three successive early stimuli are used (the so-called R-on-T
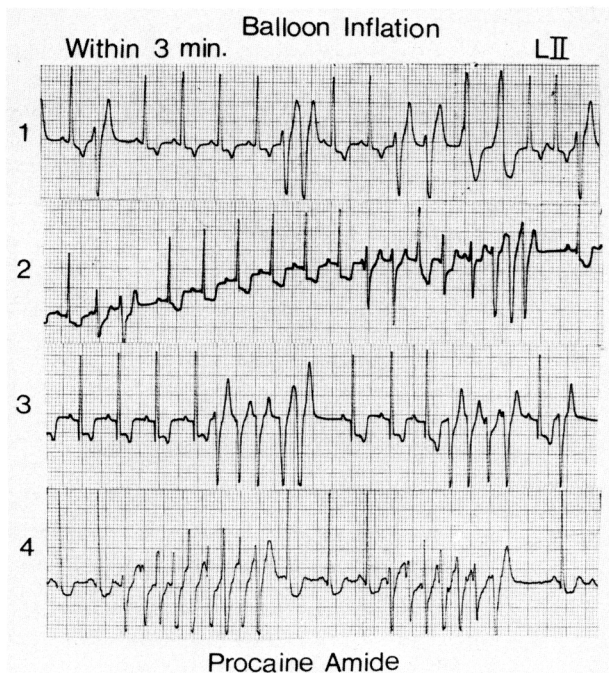
Balloon Inflation
Within 3 min. LII

Procaine Amide

FIGURE 1. *Within 3 minutes of acute occlusion of the left anterior descending coronary artery in the awake dog, there are paroxysms of rapid ventricular tachycardia. While the prevalence of arrhythmia in the procainamide-pretreated is undiminished compared to the control ligation, the occurrence of ventricular fibrillation is markedly reduced.*
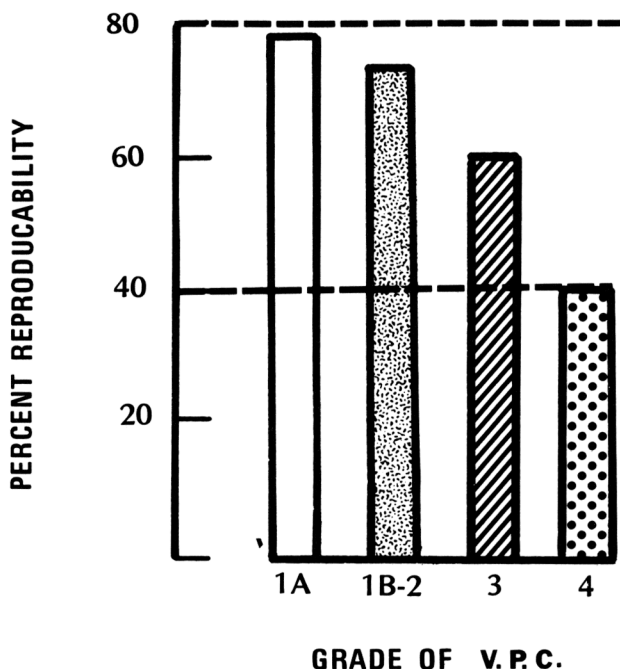

FIGURE 2. *The reproducibility of a single 24-hour monitoring session was assessed in a repeat study of 65 patients. While low grades of ventricular premature complexes (VPCs) were highly reproducible, this was not the case with advanced grades.*[19]

pulsing technique), small physiologic currents are sufficient to provoke VF.[20, 21] Within approximately 2 minutes after the left anterior descending coronary artery is abruptly occluded in the closed-chest dog, sequential R-on-T pulsing shows a striking drop in threshold for VF and a lengthened duration of the vulnerable period (table 2).[21] These changes are transient; within 4.5 minutes, the threshold returns to preocclusion levels. Similar changes follow reperfusion, upon abrupt deflation of the occluding balloon; however, these alterations in cardiac vulnerability are smaller and briefer. The time course of these changes and the altered susceptibility to VF parallel the emergence and recession of arrhythmias after coronary artery occlusion and release (fig. 3).

An end point of VF is impermissible as an index of electrical instability in man: A more innocuous marker is required. We have found that the evocation of two responses to a single stimulus discharged during the ventricular vulnerable period is a sensitive indicator of susceptibility to VF. The awake animal exhibits no overt evidence of awareness of such testing. Repetitive ventricular responses occur reproducibly when 66% of the fibrillatory current has been administered. The nadir of the repetitive extrasystole threshold in the cardiac cycle coincides with the vulnerable period for VF during various maneuvers that alter cardiac susceptibility to this arrhythmia[22] (fig. 4).

The population that has myocardial electrical instability from which SCD victims are drawn probably includes several million people. To screen such multitudes for repetitive ventricular responses requires simple, noninvasive methods. In animals, therefore, we have tested mechanical precordial thumping as a possible method for exposing electrical instability.[23] Indeed, we have found that a mechanical thump may induce ventricular arrhythmia (fig. 5). The basis for effectiveness of such stimulation is depolarization of myocardial fibers by transduction of the mechanical pulse into an electrical pulse.[24] The heart responds as a mechano-electrical transducer. By the use of sequential R-on-T pulsing, the provocation of repetitive extrasystoles may serve as an indicator of the presence of a reduced threshold for VF. While these studies are preliminary, they do suggest a possible direct ap-

TABLE 2. *Threshold for Ventricular Fibrillation in 10 Dogs During 10-minute Occlusion and Release of the Left Anterior Descending Coronary Artery Measured by Sequential R/T Pulsing*

Period of study	Threshold (mA)	Vulnerable period duration (msec)	Duration of reduced threshold (min)
Control	56 ± 7.1	14 ± 7	—
Occlusion	1.6 ± 0.3*	76 ± 37	4.6 ± 0.3
Release	3.6 ± 1.8*	26 ± 7	2.1 ± 0.4

Values are mean ± SEM.
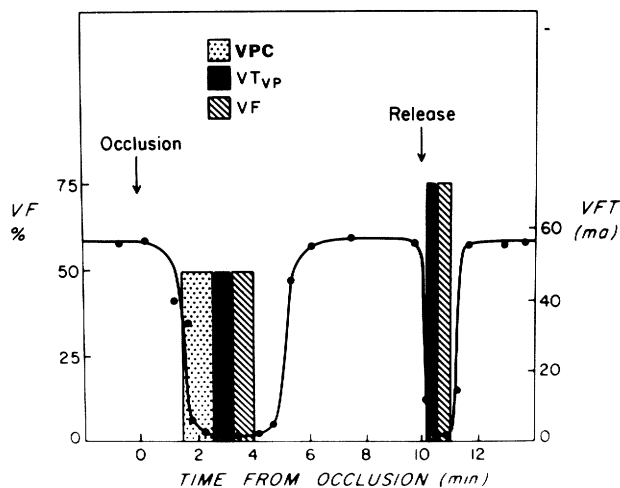*$p < 0.001$ from control (t test).

FIGURE 3. Effect of acute coronary artery occlusion and release on the susceptibility to ventricular fibrillation (VF) as related to the spontaneous occurrence of diverse ventricular arrhythmias. The predisposition to VF, measuring the ventricular fibrillation threshold (VFT) in man, is accomplished by triple R/T pulsing. Note the correspondence between changes in VFT and the occurrence of arrhythmias.[21] VPC = ventricular premature complex; VT = ventricular tachycardia.

FIGURE 5. An external mechanical stimulus induces a repetitive extrasystole (↓) analogous to that evoked by electrical stimulation with an intracardiac catheter in a dog after acute myocardial infarction.
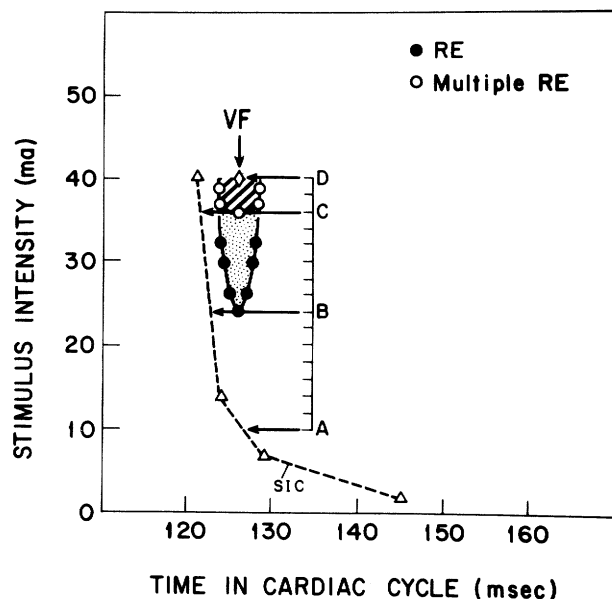

FIGURE 4. Relation of repetitive extrasystole (RE) and ventricular fibrillation (VF) thresholds determined by scanning the vulnerable period with a 2-mA, constant-current cathodal stimulus. Electrical diastole was scanned in 1-msec decrements beginning 10 msec after the T wave and ending at the border of the strength-interval curve (SIC) (left line). The provocation of RE (B) required 66% of the current for VF while multiple RE (C) occurred with 82%. Vulnerable-period curves for RE and multiple RE have a characteristic "V" shape, the nadir of which coincides temporally with that for provoking VF.[22]
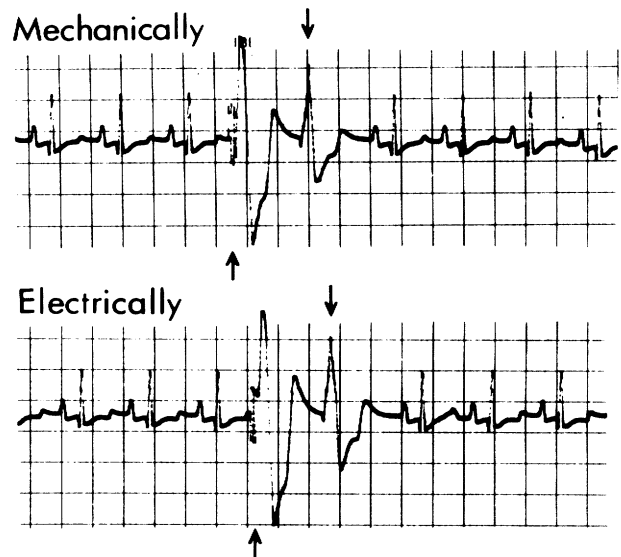
proach for determining the existence of myocardial electrical instability in man.

Protection Against SCD

It is already becoming possible to protect the patient who has been resuscitated from VF against recurrence of cardiac arrest.[25, 26] Essential elements of a prophylactic program involve the use of antiarrhythmic drugs. Therapy, however, needs to be individualized. The objective of treatment is reduction in frequency or complete abolition of advanced grades of VPCs rather than suppression of all ectopic activity. Ambulatory monitoring as well as exercise stress testing are used to detect VPCs and to gauge the therapeutic efficacy of selected antiarrhythmic measures. In a recent experience with 70 patients with recurring malignant ventricular arrhythmias, individualized treatment has prevented, in a majority, the recurrence of these life-threatening disorders. The annual mortality has not exceeded 5% among patients whose advanced grades of VPCs were controlled.

Institution of appropriate therapy is time consuming and costly and is not yet guided by sound electrophysiologic principles. However, there is no current substitute for intelligent pragmatism. The physician is committed to protect patients entrusted to his or her care. Developments in both pharmacology and electrophysiology have been rapid and promise to improve the scientific basis for prophylaxis against SCD.

Precipitating Factors of VF

If electrical instability of the myocardium long antedates the occurrence of SCD, there must be factors that precipitate VF. Current cardiovascular research has focused almost exclusively on the electrophysiologic abnormalities in the heart that are con-

ducive to sustained repetitive ventricular activity. Scant attention has been devoted to the operation of transient risk factors that favor the emergence of catastrophic arrhythmia. Among many factors that may induce VF, nervous impulses to the heart are probably of critical importance.[27, 28] If these relations are corroborated in man, new therapeutic possibilities will soon emerge.

Evidence Relating Neural Factors to Arrhythmia

The most important subcortical regions involved in regulating cardiac rhythm are located in the hypothalamus and quadrigeminal bodies. In normal hearts, brain stimulation at specific sites does not provoke VF. However, in dogs with acute myocardial ischemia, VF is consistently induced when the posterior hypothalamus is stimulated.[29] The fibrillation threshold is lowered after such stimulation, even when concomitant changes in arterial pressure and heart rate are prevented.[30] When the stellate ganglia, way stations in sympathetic neural connections from brain to heart, are stimulated, R-on-T pulsing of the right ventricle with twice threshold currents provoked VF in 60% of animals.[30] In the absence of stimulation of these ganglia, R-on-T pulsing never induced VF. Protection against VF has also been shown by reflex lessening of sympathetic tone achieved by raising blood pressure by injection of the α-adrenergic-stimulating drug phenylephrine. This has been noted in the normal animal as well as in dogs during acute coronary artery ligation.[31]

There is evidence that sympathetic neural traffic to the heart can be diminished by administering serotonin precursors that localize in the central nervous system.[32, 33] We examined the question whether manipulation of central nervous system serotonin can affect cardiac vulnerability. Dogs were given the serotonin precursors L-tryptophan or 5-hydroxy-L-tryptophane in conjunction with the monoamine oxidase inhibitor phenelzine and the selective L-amino acid decarboxylase inhibitor carbidopa.[34] Tryptophan, an essential dietary amino acid, is the physiologic, biochemical precursor of serotonin. When tryptophan alone is administered, it is hydroxylated and then decarboxylated to form serotonin at sites throughout the body. Monoamine oxidase then catalyzes a rapid degradation of the serotonin. The objective of these experiments was to concentrate serotonin in the brain but not in the periphery. This was accomplished by the simultaneous administration of phenelzine and carbidopa. Phenelzine inhibits monoamine oxidase so that serotonin tends to accumulate whenever it is formed. Carbidopa is an L-aromatic amino acid decarboxylase inhibitor that circulates in the periphery, but does not cross the blood-brain barrier. In the presence of carbidopa, the decarboxylation of tryptophan is selectively diminished peripherally and therefore the accumulation of serotonin is largely restricted to within the central nervous system. Ventricular vulnerability was evaluated in these animals by measuring the repetitive extrasystole threshold. A sustained increase in repetitive extrasystole threshold

of 50% resulted only when we used biochemical measures that presumably increase central nervous system serotonin. These findings suggest that neuropharmacologic measures perhaps affecting central sympathetic activity can alter cardiac vulnerability and may protect against VF.

Psychologic Variables and VF

A major goal of our studies has been to determine whether behavioral and psychologic factors can change cardiac vulnerability and thereby predispose to VF. Dogs were exposed to two environments: a cage in which the dog was left largely undisturbed and a Pavlovian sling in which the dog received a single 5-J transthoracic shock at the end of each experimental period for three successive days.[35] These two environments were compared on days 4 and 5. At these times, the dogs placed in the sling became restless, they frequently salivated excessively, exhibited somatic tremor, and had a mean heart rate of 136 beats/min. In the cage, the mean current that elicited repetitive extrasystoles was 43 mA ($\pm$ SEM). In the sling, the mean threshold was reduced to 14 ± 6 mA ($p < 0.001$). During these studies, heart rates were held constant by cardiac pacing. These findings indicate that psychologic stress can profoundly reduce the cardiac threshold for VF.

The question of whether a psychologically aversive environment may provoke arrhythmia without electrical stimulation of the heart was examined after coronary occlusion in dogs. The animals were conditioned as described above. After 5 consecutive days in which they spent an hour in the cage and an hour in the sling, a balloon occluder, previously implanted around the left anterior descending coronary artery, was inflated. Once the animals had recovered from occlusion and were entirely free of arrhythmia, they were again exposed to the two environments. The sling condition consistently provoked diverse ventricular arrhythmias, including ventricular tachycardia and early extrasystoles with T-wave interruption. These effects disappeared when the dogs were returned to the non-aversive cage.[36]

In current experiments, we have shown that when occlusion of the left anterior descending coronary artery is accomplished while the dogs are in the non-aversive environment of the cage, there is a low incidence of arrhythmia — only one of 12 dogs developed VF. However, six of the dogs developed VF when the coronary artery was occluded while the dog was standing quietly in the sling (figs. 6A and B) (Lown B, Verrier R: unpublished observations).

To test whether changes in vulnerability induced by psychologic stress could be prevented by pharmacologic blockade of adrenergic activity, dogs were exposed to programmed signal shock avoidance.[37] Behaviorally induced changes in cardiac excitability were completely abolished by the selective β-1-adrenergic blocking agent tolamolol hydrochloride. Thus, increase in ventricular vulnerability associated with aversive psychologic conditioning appears to be
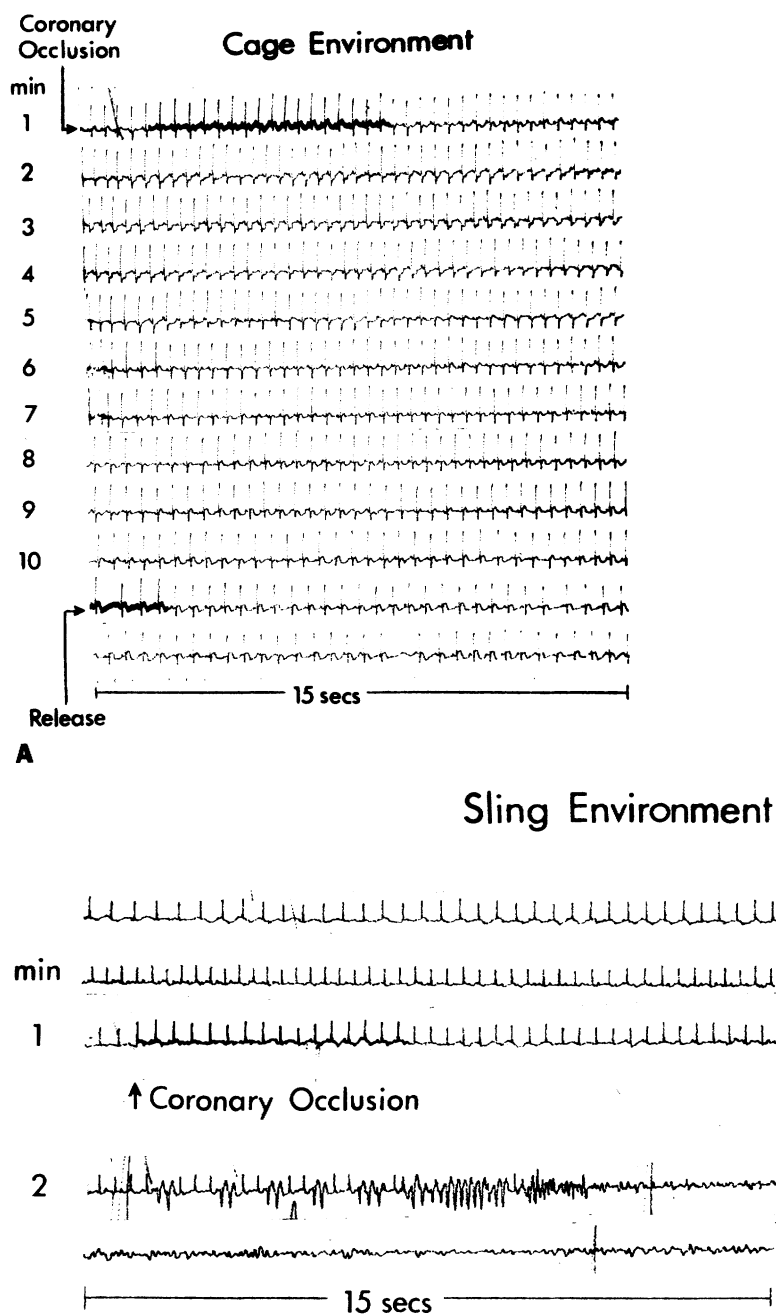
FIGURE 6. *A) When the dog is in the tranquil cage environment, acute left anterior descending coronary artery occlusion does not induce any ventricular arrhythmia upon inflation or deflation of the occluding balloon catheter. B) When the dog is in the aversive environment of the sling, acute coronary artery occlusion provokes ventricular fibrillation in less than 2 minutes.*

mediated primarily by the sympathetic limb of the autonomic nervous system.

Clinical Considerations

Physicians have long been aware that psychologic stress can provoke arrhythmias. In widely differing cultures, folklore associates sudden death with psychologic stress, excitement or intense emotion. Taggart et al.[38] conducted a systematic exploration of the relation between diverse stresses and the cardiovascular apparatus in patients with ischemic heart disease. A stress such as public speaking induced profound ST-segment depression and multiform VPCs. These changes could be prevented by pretreatment with the β-adrenergic blocking drug oxyprenolol. Emotional stress has now been shown to trigger VF in the absence of demonstrable heart disease.[39] If psychologic factors predispose to ventricular arrhythmia by increasing the level of sympathetic tone affecting the heart, diminishing of neural sympathetic activity should reduce the incidence of SCD. Several recent studies[40-42] indicate that in patients who had recovered from acute myocardial infarction, the incidence of sudden death was significantly reduced with the use of β-adrenergic blocking drugs.[40-42]

Rapidly cumulating scientific and clinical insights indicate that containment of the problem of SCD is

within reach. Like the resolution of any medical problem, there must be commitment of sufficient resources. The underlying electrophysiologic lesions contributing to electrical instability need to be defined. Noninvasive screening methods need to be developed for identifying the subject at increased risk for SCD. The key transient risk factors that can trigger VF must be catalogued. The role of higher nervous activity affecting cardiac rhythm in man needs to be explored. The development of safe, effective and long-acting antiarrhythmic drugs presents an immediate challenge.

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