Sudden Cardiac Death: The Major Challenge Confronting Contemporary Cardiology

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In the industrially developed countries, sudden cardiac death is the leading cause of death. It was recognized at the dawn of recorded history and even depicted in Egyptian relief sculpture from the tomb of a noble of the Sixth dynasty approximately 4,500 years ago. Sudden cardiac death has left no age untouched. Sparing neither saint nor sinner, it has burdened man with a sense of uncertainty and fragility. The enormity of this problem demands attention. In the United States, sudden cardiac death claims about 1,200 lives daily, or approximately one victim every minute. It is the leading cause of death among men aged 20 to 64 years, accounting for 32 percent of the fatalities in this group. Nearly 25 percent of persons dying suddenly have had no prior recognized symptoms of heart disease.[1–6] The excess of widows observed in retirement communities is accounted for by the three- to fourfold greater incidence of sudden cardiac death among men. Sudden death in old age might be a blessing rather than a scourge, but instead it frequently explodes a man's life at its prime, at a median age of only 59 years.

The medical profession has sensed the issue but has largely ignored sudden death as a problem amenable to solution. This indifference has not been the result of a lack of interest or concern but a reflection of the belief that sudden cardiac death was the inevitable culmination of coronary atherosclerosis. Because sudden death was unpredictable and afflicted the apparently healthy subject outside the hospital, the physician considered it an act of fate before which he was largely helpless. The advent of the coronary care unit has promoted a reassessment of this complex problem. It has become clear that sudden death is not the inexorable culmination of advanced coronary atherosclerosis but instead is the result of ventricular fibrillation and therefore is readily reversible.[7,8] If ventricular fibrillation were only the consequence of severe coronary atherosclerosis, once reversed it would promptly recur. However, patients treated for ventricular fibrillation seldom have recurring episodes, and they usually recover and survive for long periods.[9,10] The new concept that ventricular fibrillation is an electrical accident suggests that its cause is not anatomic and thereby contributes to the growing interest in redefining the basis for sudden death and developing methods for its containment.

Until recently our inability to deal with sudden cardiac death has not been due to a gap in the application of knowledge but to a gap in knowledge itself. The purpose of this review is to indicate how much we know and to sketch the path of possible further progress.

TABLE I

Features of the Syndrome of Sudden Cardiac Death

Heart disease	Ischemic
Place of occurrence	Community
Prodromes	Absent
Onset	Instantaneous
Acute coronary artery thrombosis	≃5%
Acute myocardial infarction	<20%
Myocardial electrical instability	Present
Recurrence rate (annual)	30%

Approaches to the Containment of Sudden Cardiac Death

The coronary care unit provided the basis for two entirely different therapeutic strategies[11]: (1) to reach the patient expeditiously at the very onset of the terminal attack in order to effect successful resuscitation, and (2) to identify the potential victim and initiate prophylactic measures against fatal arrhythmia.

Out-of-hospital cardiopulmonary resuscitation: A properly organized community effort can save a substantial number of persons from sudden cardiac death. The program conducted in Seattle, Washington demonstrated that during a 6 year period, of 1,710 ventricular fibrillation episodes, there were 346 long-term survivors.[12] These significant studies make clear that sudden cardiac death is not related to acute myocardial infarction. The incidence of acute transmural myocardial infarction (development of new Q waves) was documented in only 19 percent of patients during hospitalization after resuscitation from ventricular fibrillation. However, 75 percent of these patients had severe multivessel coronary involvement, 20 percent had miscellaneous heart disease and 5 percent had no cardiac impairment. Numerous pathomorphologic studies agree that there are few acute lesions either in the coronary arteries or the myocardium.[13–20]

Clinical studies suggest the existence of a sudden cardiac death syndrome (Table I), the key element of which is an electrophysiologic derangement that is largely the result of chronic ischemic heart disease. The myocardium is susceptible to repetitive activity. On monitoring a multitude of ventricular ectopic complexes may be detected. Death when it occurs is instantaneous and unheralded by any distinctive prodromes. When such patients are resuscitated from cardiac arrest, they are predisposed to recurrent ventricular fibrillation, with a mortality rate of 26 percent in the ensuing year and 36 percent at 2 years.[21,22]

The problem of sudden cardiac death includes two aspects: the operation of an acute precipitating trigger and the presence of chronic electrical instability of the myocardium. Patients successfully resuscitated, therefore, cannot be assured that they will be as fortunate the second time. Our view has been that the only long-range solution is the identification and protection of the potential victim.[8,11]

Identification of the subject at risk: The risk factors for atherosclerosis, although they indicate enhanced susceptibility to coronary disease, do not singly or in combination identify a subset of patients prone to sudden death.[2–5,23,24] Because the mechanism of sudden death is invariably ventricular fibrillation, it is logical to assume that arrhythmias serve as harbingers.[11] Experience with patients who have acute myocardial infarction in coronary care units has shown the important relation of ventricular premature complexes to the development of more serious cardiac arrhythmias and early death.[25,26] Numerous recent reports associated the presence of ventricular ectopic activity during longer monitoring intervals with an increased risk of sudden cardiac death out of the hospital.[27–36] However, prolonged ambulatory monitoring demonstrates that nearly 90 percent of patients with coronary heart disease exhibit ectopic activity.[37] Thus, the mere presence of ventricular arrhythmia cannot be a significant prognostic discriminator of risk for subsequent fatality. It has been our view that ventricular premature complexes need to be graded according to frequency, persistence, multiformity, repetitive pattern and degree of prematurity.[8]* Only frequent advanced grades or complex forms of ventricular premature complexes enhance the risk of future sudden cardiac death in patients with coronary heart disease.[38]

The Ventricular Premature Complex Hypothesis

A number of crucial questions need to be answered if the "ventricular premature complex hypothesis" is to guide clinical practice: (1) Does the epidemiologic evidence decisively confirm that the ventricular premature complex predicts increased risk for sudden cardiac death? (2) If enhanced risk is demonstrated, is it related to the mere presence or to the grade of ventricular premature complex? (3) Do advanced grades of ventricular premature complexes indicate only the severity and extent of ischemic heart involvement? (4) Finally, and perhaps most importantly, does control of ventricular premature complexes protect against the risk of ventricular fibrillation?

Ventricular Premature Complexes and the Risk for Sudden Cardiac Death

One of the earliest comprehensive investigations that related ventricular premature complexes to the occurrence of sudden death was the Coronary Drug Program Study.[39] This study was a long-term, randomized double-blind trial involving 8,341 recruited male survivors of myocardial infarction that aimed to evaluate the effectiveness and safety of lipid-lowering drugs in prolonging the survival of patients with ischemic heart disease. Eligible men ranged in age from 30 to 65 years at the time of enrollment and had survived their most recent infarction for at least 3 months. One third (2,789) were assigned randomly to a placebo treatment group. Complete edited baseline data for all measured vari-

* *The following grading system has been used:* 0, none; 1A, occasional, isolated ventricular premature complexes (less than 1/min, less than 30/hr); 1B, occasional, isolated ventricular premature complexes (greater than 1/min, less than 30/hr); 2, frequent ventricular premature complexes (greater than 30/hr); 3, multiform; 4A, couplets; 4B, salvos of three or more; 5, early ventricular premature complexes (abutting or interrupting the T wave).

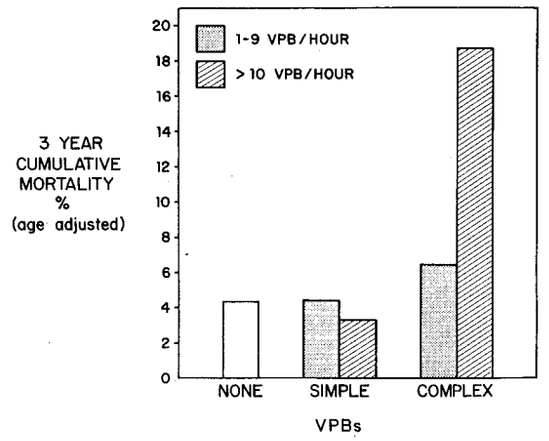

FIGURE 1. Cumulative sudden death among 1,739 men with prior myocardial infarction monitored for 1 hour. The mortality rate increases sharply only in patients with frequent complex ventricular premature complexes (VPB). The presence of ventricular premature complexes, even when they are frequent, is not an indicator of risk. (Adapted from Ruberman et al., with permission of the author and publisher.)[38]

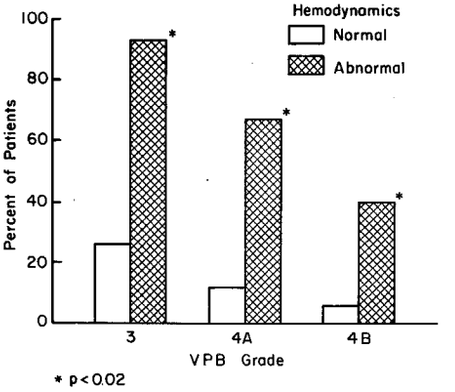

FIGURE 2. Maximal grade of ventricular premature complexes (VPB) during 24 hour monitoring compared in 15 patients with coronary heart disease, asynergy and increased left ventricular end-diastolic pressure (abnormal group) and in 34 patients without these abnormalities (normal group). Note the striking difference in the distribution of advanced grades of arrhythmia. The occurrence of grade 4B arrhythmia, that is, salvos of ventricular tachycardia, was eight times greater in the abnormal than in the normal group. (From Calvert et al., with permission of the publisher.)[42]

ables were available from 2,035 of these men, who made up a cohort subsequently followed up for 3 years. Among these, 235 men (11.5 percent) had one or more ventricular premature complexes in their resting baseline electrocardiogram. During the follow-up period, there were 256 deaths, which were twice as frequent in patients with ventricular premature complexes (21.7 percent) as in those free of ectopic activity (11.4 percent). The increased long-term risk of death, including sudden death, was associated with the frequency of ventricular premature complexes with couplets and runs (grade 4) and possibly with early cycle ectopic complexes. The increased risk associated with these advanced grades of ventricular premature complexes was independent of 28 other variables related to baseline electrocardiographic and clinical characteristics.

A systematic investigation analyzing the relation between advanced grades of ventricular premature complexes and sudden death is being conducted by Ruberman et al.[30] This ongoing epidemiologic study of the Health Insurance Plan of New York involves 120,000 men aged 35 to 74 years. From a subset of patients with prior myocardial infarction, 1,739 were monitored for 1 hour while sedentary and then followed up for an average period of 24.4 months for mortality. Patients with complex ventricular premature complexes (R-on-T, runs of two or more, multiform or bigeminal) in the monitoring hour had risk for sudden cardiac death three times greater than that of patients free of such arrhythmia. A most significant finding was that the mere presence of ventricular premature complexes, even when frequent, did not increase the likelihood of sudden fatality. Thus among patients with ventricular premature complexes, the cumulative occurrence of sudden death during a 3 year period was 4.2 percent, which was no different than the mortality rate among those without ectopic activity. However, the presence of advanced grades of ventricular premature complexes was associated with a 15.5 percent incidence rate of sudden cardiac death during the 3 year follow-up period (Fig. 1).

Ventricular Premature Complexes and Extent of Coronary Heart Disease

In the cited study above,[30] mortality as well as frequency of ventricular premature complexes increased sharply with age. In addition, the prevalence of ectopic activity, as also noted by others, was related to the extent of myocardial damage.[40,41] This relation was explored by Calvert et al.[42] They performed 24 hour electrocardiographic monitoring of 125 ambulatory patients before cardiac catheterization and coronary angiography and found ventricular premature complexes in 83 percent. Ectopic activity, which persisted for at least 3 of the 24 hours, was noted in 75 percent of the 84 patients with documented coronary artery disease, in 61 percent of the 28 patients with other heart disease and in 24 percent of the 12 normal subjects. Increased prevalence and grade was significantly more frequent in patients with multivessel disease than in patients with only one vessel involvement. The latter group did not differ from those without coronary disease in frequency and distribution of ventricular premature complexes. The presence of elevated left ventricular end-diastolic pressure and one or more zones of asynergy was associated with increased ventricular ectopy (Fig. 2). Paroxysms of ventricular tachycardia were noted in 40 and 67 percent, respectively, of the patients with combined asynergy and elevated left ventricular end-diastolic pressure (19 mm Hg or greater) but in only 6 and 12 percent, respectively, of the patients without these hemodynamic abnormalities ($P < 0.005$).

Similar findings were reported by Schulze et al.,[28] who monitored a smalll number of patients after recovery from acute myocardial infarction who had car-

diac catheterization during their late hospital phase. The patients with complicated ventricular arrhythmias (multiform, couplets, ventricular tachycardia or ventricular premature beats with T wave interruption) had a greater number of proximally obstructed major coronary arteries and more extensive disease than the patients with infrequent or no ectopic activity. Weaver et al.[43] reported more extensive coronary artery disease and myocardial impairment in patients with recurrent ventricular fibrillation after successful resuscitation than in those with only a single episode. Triple vessel disease (70 percent or greater stenosis) was found in 64 percent of the 14 patients with repeated malignant arrhythmia and in 22 percent of the patients with only one such event ($P < 0.01$). Those with recurrent ventricular fibrillation also had a significantly lower ejection fraction (0.39 versus 0.51) and more myocardial wall motion abnormalities.

It may be argued cogently that prognostic implications are not determined by the ventricular premature complex but by the extent of cardiac disease because the grade of ectopic activity is largely an expression of the severity of the disease. A corollary inference is that the attempt to control ventricular arrhythmia is futile because the ultimate outcome is determined by the extent of heart disease. A recent study of Schulze et al.[28] contradicts such a conclusion. Although advanced grades of ventricular premature complexes (Lown grading)[8] occurred only in patients with an ejection fraction of less than 40 percent, sudden out-of-hospital death occurred only in those with an advanced grade of ectopic activity. Thus, of 45 patients with an impaired ventricular ejection fraction, 19 were free of a significant grade of ventricular premature complex and none died in a 7 month follow-up period. In contrast, among 26 patients with similar hemodynamic deficits but with major grades of ventricular premature complexes, eight died suddenly ($P < 0.02$). It may well be that extensive cardiac disease predisposes to advanced grades of frequently recurring ventricular arrhythmia, thereby increasing the chance that sequential ectopic complexes will lower the threshold of the ventricular vulnerable period and precipitate ventricular fibrillation.

Does Control of Ventricular Premature Complexes Protect Against Sudden Death?

Before responding to this important question, it is worthwhile to detail the essential principles for managing patients with advanced grades of ventricular ectopic activity. The therapeutic intent in controlling ventricular premature complexes is not directly concerned with the overt arrhythmia, but is guided by the concept that the annulment of the arrhythmia indicates efficacy in protecting against sudden death. Although the procedure for terminating an episode of life-threatening arrhythmia is standardized and readily accomplished, the measures that afford adequate protection against ventricular fibrillation are not certain.

Any prophylactic program against sudden death must involve the use of antiarrhythmic drugs to subdue ventricular premature complexes. However, merely administering a drug to a patient in the hope of preventing fatality is frequently an exercise in futility. Schaffer and Cobb[21] found that 73 percent of 64 patients with recurrent ventricular fibrillation at the time of sudden death were receiving antiarrhythmic therapy. Thus there is a need to rationalize therapy. Neither the electrocardiographic attributes of the ventricular rhythm disorder nor the type and extent of underlying heart disease are sufficient guides for selecting a specific drug. When an antiarrhythmic drug fails to prevent the recurrence of malignant arrhythmia, it is not known whether the proper drug was used or the correct dose administered. There are additional problems in choosing an effective prophylactic agent. Ventricular premature complexes occur sporadically but rarely

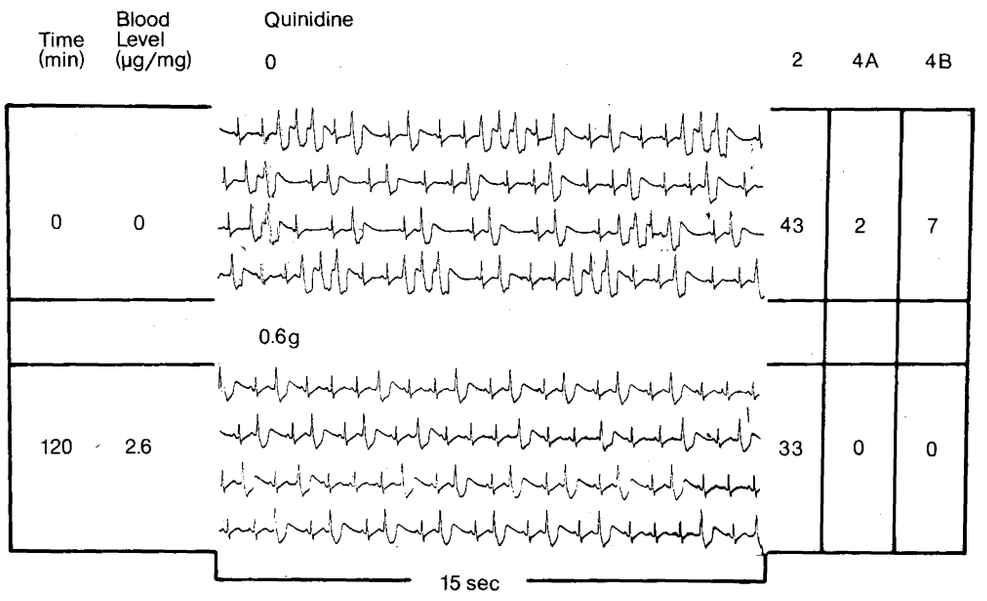

FIGURE 3. Acute drug testing (phase 1) with quinidine. Peak drug action occurred 2 hours after the ingestion of 0.6 g of quinidine. The serum level at that time was 2.6 μg/ml. Although the complexes decreased only marginally, the advanced grades were abolished, which is considered an adequate therapeutic effect.

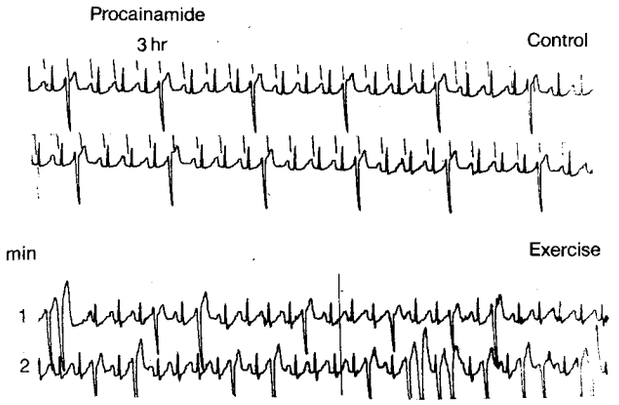

FIGURE 4. Acute drug testing with procainamide. After the administration of 1.5 g the advanced grades of ventricular premature complexes were abolished and their frequency decreased during rest **(upper tracing)**. However, with stationary bicycle exercise, ventricular premature complexes increased in frequency with the emergence of couplets and paroxysms of ventricular tachycardia **(lower tracing)**.

provoke any symptoms. Generally when an antiarrhythmic agent is used, the physician gauges therapeutic efficacy by the abatement of symptoms or the prevention of sustained and demonstrable arrhythmia. In a patient with a disordered mechanism of the heart beat but no symptoms, repeated Holter monitoring sessions are required to determine whether a drug is of value. When ectopic activity is infrequent and sporadic, it is difficult to determine, even with longer or more frequent periods of monitoring, whether the selected drug will prove effective. Dependence on such methods is costly, time-consuming and possibly without benefit. The problem is even more challenging when the patient has a life-threatening rhythm disorder because then no error in drug prescription is permissible.

Clearly, new techniques are needed for determining the effectiveness and the proper dose of a drug in controlling ventricular premature complexes in a specific patient. Because the commonly used antiarrhythmic agents may sometimes aggravate arrhythmia and thus threaten survival, the method of drug selection must also permit the prompt recognition of such potential adverse reactions.

To respond to some of these problems we approach drug selection in two phases: The first involves rapid screening of the drug to assess its short-term efficacy and safety. The second phase involves a brief maintenance program to determine the patient's tolerance and the effectiveness of the drug during long-term administration.

Phase 1 drug testing: The achievement of a significant or so-called therapeutic blood concentration is crucial to the effectiveness of many antiarrhythmic drugs.[44,45] Achieving such a concentration with a single dose constitutes phase 1 study and involves the following three elements[46]: (1) the administration of a single large oral dose of a selected antiarrhythmic drug; (2) the use of programmed trendscription to display the time course of drug action[47] (Fig. 3); and (3) sampling

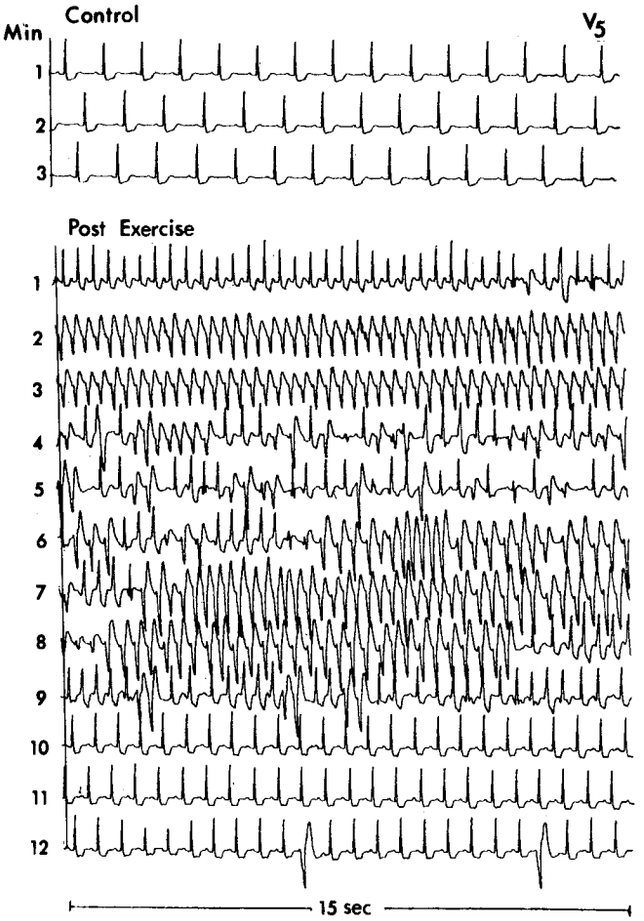

FIGURE 5. Phase 2 testing of tocainide. Repeated 24 hour periods of monitoring while the patient was receiving 1,200 mg of tocainide daily disclosed no advanced grades of ventricular premature complexes in a 52 year old man with frequently recurring ventricular fibrillation due to ischemic heart disease. However, during recovery from exercise on a motorized treadmill, prolonged salvos of ventricular tachycardia occurred but abated within 9 minutes. Trendscription records the entire exercise test.

the blood for drug concentration during this period of observation to permit correlations with the onset and dissipation of antiarrhythmic or toxic effects.

The amount of drug used generally consists of half the commonly used daily maintenance dose. Thus, the dose for quinidine is 600 mg, for procainamide 1.5 g, for propranolol 80 mg, for disopyramide phosphate 300 mg, for mexiletine 600 mg and for pindolol 10 mg. These doses proved sufficient in most patients to produce what has been deemed a therapeutic blood level.

Each patient undergoing testing undergoes 24 hour monitoring for arrhythmia and exercise stress testing. On the day of the test the patient has a 30 minute period of control trendscription to define the level of ventricular ectopic activity at rest. After the control period, exercise on a bicycle ergometer may be used to induce arrhythmia and thus assist in defining drug action. Exercise is necessary to precipitate arrhythmia in some patients who have none at rest. The patient exercises each hour for 5 minutes (Fig. 4), and trendscription

TABLE II

Antiarrhythmic Drugs Used for Maintenance Therapy in 72 Patients With Malignant Ventricular Arrhythmias

	no. of Patients
Digitalis	54
Beta-adrenergic blocking agents*	48
Quinidine sulfate	27
Diphenylhydantoin	14
Disopyramide	13
Procainamide	12
Mexiletine	6
Amiodarone	6
Tocainide	5
Aprindine	4
Bretylium tosylate	2
Lithium	2
Total	197

* Included propranolol in 39 patients, pindolol in 8 and levo-bunolol in 1.

continues during and after exercise. A control 12 lead electrocardiogram is obtained. Leads 11 and V_2, V_3 or V_4 are recorded at a paper speed of 50 mm/sec to determine the duration of the Q-T, P-R and QRS intervals. A 50 percent reduction in ventricular premature complexes and the elimination of grades 4 and 5 during the time of peak drug action is considered a positive response.

Acute drug testing, or phase 1 study, aims to define during the time course of changing drug concentration a therapeutic effect on the arrhythmia and to note any toxic complications. This continuous and intense period of observation provides much data on the possible benefits and hazards of the antiarrhythmic agent. Because only a single dose is used, the effects are short-lived and any risk to the patient is of short duration. Moreover, highly trained personnel are in attendance at all times, well equipped to deal with threatening arrhythmias. After performing a series of such tests in a patient with different drugs, one determines relatively quickly which drugs are optimally effective.

Phase 2 drug testing: The most promising agent derived from phase 1 screening is then studied further. The patient is maintained on the selected drug for 48 to 72 hours. Drug efficacy is determined with 24 hour ambulatory monitoring and maximal exercise stress testing on a motorized treadmill. The two methods are complementary; at times one technique for ventricular arrhythmia exposure suggests drug efficacy that is belied by the other (Fig. 5). Psychologic stress testing is also used to provoke arrhythmia and thereby provide additional certainty as to the adequacy of a particular drug. Blood drug levels are measured at appropriate times to compare the concentrations reached with those observed during phase 1 studies. Such a systematic approach removes some of the guesswork in antiarrhythmic management and permits the individualization of therapy to the unique requirements of the particular patient.

Our initial therapeutic objective, during both 24 hour monitoring and exercise stress testing, was to reduce ventricular premature complexes by 75 percent and abolish all grade 4 and 5 arrhythmias.[48] It soon became evident that this objective could not be readily achieved without producing an inordinate number of adverse and intolerable reactions. Our present approach is to be less concerned with the frequency of ventricular premature complexes but instead to try to suppress almost completely grade 4 and 5 arrhythmias. The presence of couplets (grade 4), if rare and fewer than one per hour during a minority of waking hours, is considered an acceptable result. However, if ventricular tachyarrhythmias with rapid rates (greater than 180 beats/min) are provoked during exercise, the drugs are manipulated until the arrhythmias are completely abolished.

The use of drug combinations is indicated in patients who have had ventricular fibrillation in the absence of myocardial infarction. To these patients, we consistently administer two antiarrhythmic drugs proved effective in phase 2 studies. This "fail safe" system of drug usage is mandated by the unacceptable price of failure. With ventricular fibrillation the physician may not have the opportunity to remedy a therapeutic error.

A total of 14 antiarrhythmic agents were screened in 72 patients with malignant ventricular arrhythmias (either ventricular fibrillation or ventricular tachycardia with syncope), and an average of 2.7 drugs was used in each patient (Table II). A major problem was the high incidence of adverse drug reactions. We were therefore impressed with Ethmozin®, a drug developed several years ago in the USSR. It is a phenothiazine derivative with slow latency in onset of action and efficacy against ventricular arrhythmias. Morganroth et al.[49] administered Ethmozin in 14 patients with frequent ventricular premature complexes in a dose of 2.4 to 11.2 mg/kg per day. The protocol involved the administration of placebo for 3 days, Ethmozin for 7 days and placebo for 3 days. During each of these 13 days patients underwent 24 hour ambulatory Holter monitoring. Ten of the 14 patients had a greater than 60 percent decrease in ventricular premature complexes ($P < 0.05$). Podrid, Lyakishev, Lown and Mazur (unpublished observations) in an investigation in Moscow (part of the USA-USSR Cooperative Health Agreement in Problem Area No. 5—Sudden Death) studied 26 patients with high frequency ventricular arrhythmias. Both phase 1 and phase 2 studies were used. The dose of Ethmozin was 200 mg three times daily. Fourteen of the patients (54 percent) had a mean decrease of 67 percent or greater in the frequency of ventricular premature complexes and the complete elimination of advanced grades. Only minor side effects occurred in four patients.

Digitalis drugs and ventricular premature complexes: It was recently suggested that digitalis drugs may be valuable in suppressing ventricular arrhythmias.[50] Acetyl strophanthidin was administered to 142 patients with frequent ventricular premature

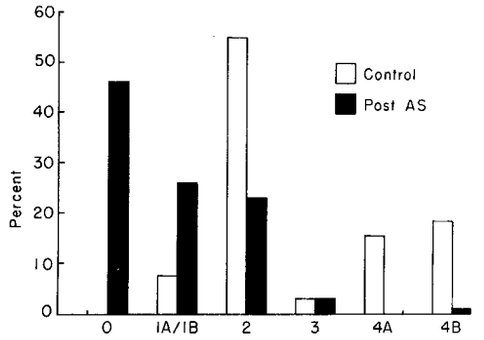

FIGURE 6. Shift to the left or to lesser grades of ventricular premature complexes after the administration of acetyl strophanthidin (AS) in 65 patients. Although grades 1A and 1B (or infrequent ectopic beats) increased, grade 4A was abolished and grade 4B was almost entirely suppressed. At the time of peak drug action all ectopic activity was abolished in 30 patients (45 percent). (From Lown et al., with permission of the publisher.)[50]

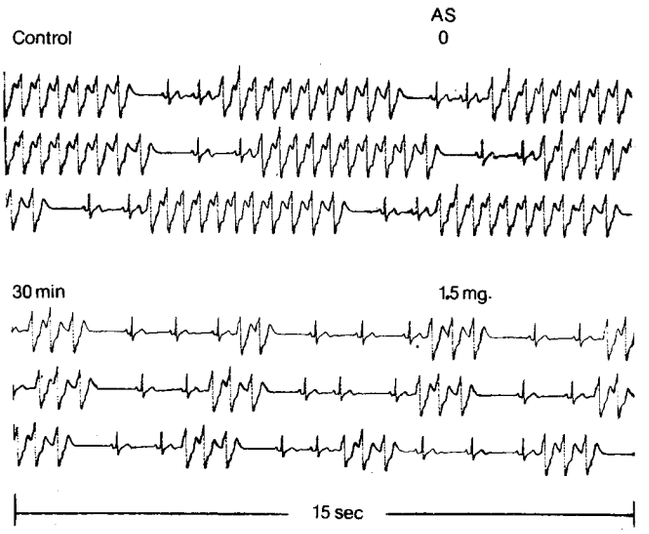

FIGURE 7. Effects of acetyl strophanthidin (AS) in a young woman without structural heart disease but with ventricular tachycardia that was almost continuous and refractory to most drugs. After the administration of 1.5 mg of acetyl strophanthidin, the salvos decreased from 10 to 12 beats to 2 to 3 beats. Antiarrhythmic drugs abolished ventricular tachycardia after digitalization with digoxin.

complexes (greater than 1/min). In 65 of these patients (46 percent), there was a significant decrease in the frequency of ventricular premature complexes and a noteworthy shift to lower grades. At the time of peak drug action ventricular premature complexes decreased by 82 percent and disappeared entirely in half of the patients (Fig. 6). Our experience to date indicates that in some patients digoxin therapy produces the same results as therapy with acetyl strophanthidin.[51] We also noted that digitalization may enhance the efficacy of other antiarrhythmic drugs (Fig. 7).

If these preliminary observations are confirmed, the treatment of ventricular arrhythmias will be simplified. A therapeutic blood level of the digitalis glycosides can be maintained with a single daily dose. Patient acceptance is good and toxic side effects are largely dose related. Furthermore, medical experience, extending now for nearly two centuries, has provided familiarity with the prescription of digitalis as well as certainty that serious adverse reactions will not occur after prolonged use.

Does Control of Advanced Grades of Ventricular Premature Complexes Prevent Sudden Death?

This is by far the most crucial question relating to the treatment of ventricular premature complexes. An answer can be obtained most readily by studying patients with recurring malignant ventricular arrhythmias such as ventricular fibrillation, paroxysmal ventricular tachycardia with syncope or sustained ventricular tachycardia that results in hemodynamic compromise jeopardizing immediate survival. We treated 72 patients with these rhythm disorders, 55 men and 17 women. Forty-five of these patients had documented coronary artery disease, and 17 had miscellaneous cardiac problems (5 had flail mitral valve syndromes; 3 had cardiomyopathy; and 3 had congenital, 2 rheumatic, 1 hypertensive and 3 unknown forms of heart disease). In 10 patients, no abnormality was found in either the myocardium or the coronary artery during an extensive work-up (Table III). The 62 patients with heart disease were followed up an average of 19.2 months after the initiation of antiarrhythmic measures. In each patient phase 1 and 2 antiarrhythmic drug studies as well as acetyl strophanthidin drug testing were performed.

In the group of 10 patients without heart disease, the proportion of women was higher and the age much younger than in the other groups. No patient in this

TABLE III

Some Clinical Features of 72 Patients With Malignant Arrhythmia

Clinical Diagnosis	no. of Patients	Sex		Mean Age (yr)	Recurrent Ventricular Fibrillation	Ventricular Tachycardia	
		Male	Female			Syncope	Sustained
Coronary artery disease	45	40	5	56	28	6	11
Miscellaneous heart disease	17	10	7	44	9	1	7
No heart disease	10	5	5	36	5	4	1

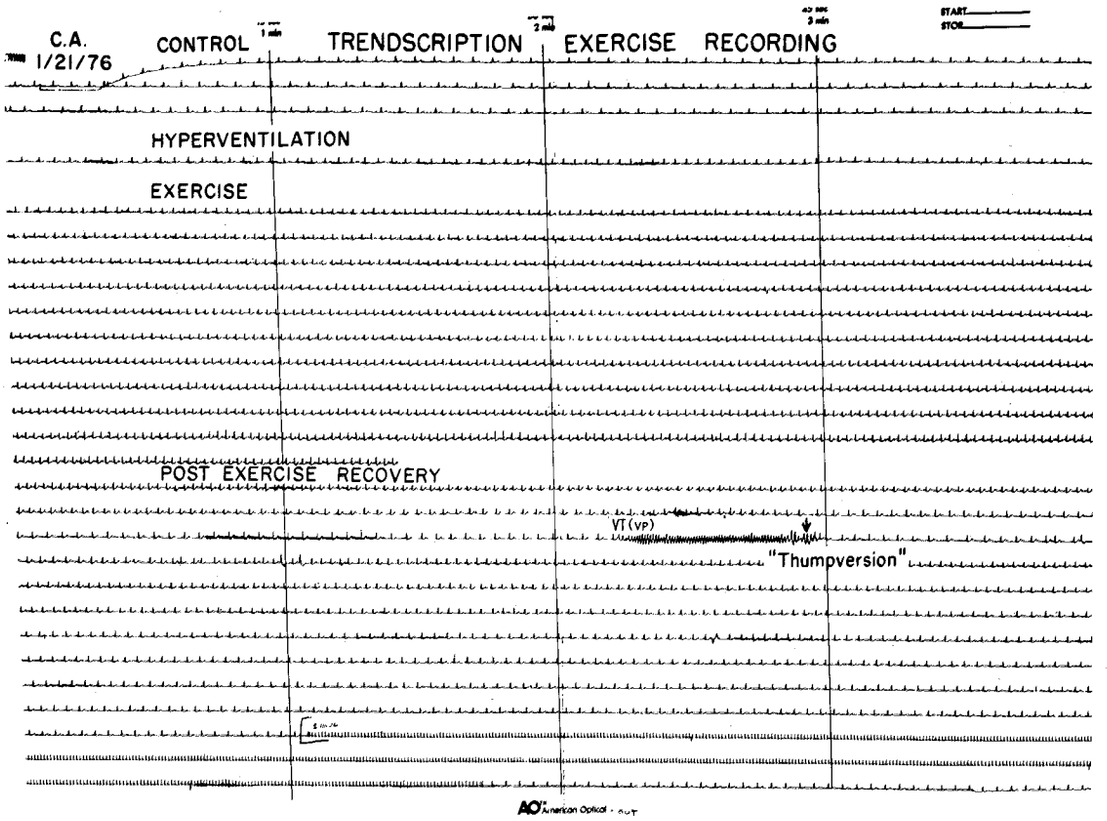

FIGURE 8. Exercise testing after the withdrawal of antiarrhythmic drugs. Complete continuous recording of the exercise test; each line represents 1 minute of monitored information. No arrhythmia occurred during 10 minutes of exercise testing on a motorized treadmill using the Bruce protocol. Within 2.5 minutes of the recovery period, there was a burst of ventricular tachycardia of the vulnerable period (VT [vp]) and degeneration to ventricular fibrillation. A single thump **(arrow)** restored sinus rhythm.

group had further arrhythmia after the initiation of a therapeutic program, although five had had earlier ventricular fibrillation refractory to prophylactic measures. One of these patients required more than 50 cardiopulmonary resuscitations but was entirely free of arrhythmia during a 4 year follow-up period.

Thirty-two of the 45 patients (71 percent) with coronary disease achieved control of arrhythmia; that is, grade 4B arrhythmia was eliminated, grade 4A was almost eliminated and total ectopic activity was reduced by 50 percent. Such a therapeutic end point was also achieved in 14 of 17 patients (82 percent) with miscellaneous forms of heart disease. In both of these groups, control of arrhythmia was associated with a striking survival record during the follow-up period. The 46 patients judged to have been effectively treated for ventricular premature complexes had a 3.9 percent annual incidence rate of sudden cardiac death. In contrast, of the 16 patients with advanced grades of arrhythmia that were not controlled, 37.5 percent died suddenly ($P < 0.01$). Among the 32 patients with coronary heart disease whose arrhythmia was controlled, only 1 sudden death occurred during a 17.9 month follow-up period. The single death in this group occurred suddenly 2 days after the patient was brutalized during a hold-up. If the anticipated mortality rate for patients successfully resuscitated from a single episode of ventricular fibrillation[12,21] were projected on these 32 patients with ischemic heart disease, approximately 10 patients rather than 1 would be expected to have a potentially fatal arrhythmic episode during the follow-up period. Because these patients were referred for frequently recurring episodes of malignant arrhythmia, the mortality in absence of adequate treatment would have been substantially greater.

In these patients the use of antiarrhythmic drugs appears to have been the key factor promoting survival. Ethical imperatives preclude withdrawing these drugs to prove their decisive role. A unique observation was provided by one patient, a 52 year old man with previous myocardial infarction followed by malignant ventricular arrhythmia. After 2 years of successful control, he insisted that he no longer required the antiarrhythmic measures. In the past, while receiving no drugs he had been free of significant arrhythmia during repeated 24 hour ambulatory monitoring sessions; only exercise stress testing exposed malignant arrhythmia. Antiarrhythmic drugs were therefore discontinued for 24 hours and he was re-exercised. Three minutes after exercise an episode of ventricular fibrillation developed that responded promptly to thump version (Fig. 8). Previously while receiving antiarrhythmic drugs the patient had been exercised numerous times to a similar or higher level without demonstrating ventricular pre-

TABLE IV

Indication for Treating Ventricular Premature Complexes

1. Primary ventricular fibrillation unprovoked by acute myocardial infarction.
2. Myocardial infarction within the past year and grade 4 or 5 ventricular premature complexes on 24 hour monitoring.
3. Angina pectoris of new onset with an advanced grade of ventricular premature complexes (grade 4 or 5).
4. Coronary heart disease and ventricular tachycardia of the vulnerable period on monitoring.
5. Coronary heart disease and grade 4 or 5 ventricular premature complexes and S-T segment depression of 2 mm or greater on peak exercise.
6. Prolonged Q-T syndrome, ventricular premature complexes and syncope.
7. Mitral valve prolapse, syncope and an advanced grade of ventricular premature complexes.
8. Advanced grade of ventricular premature complexes during angina pectoris.
9. Arrhythmia causing severe symptoms.

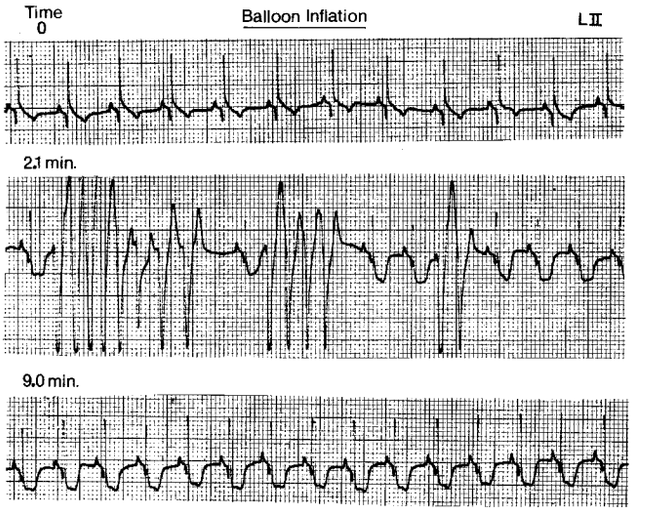

FIGURE 9. Protection against ventricular fibrillation without reduction in ectopic activity. Balloon inflation and occlusion of the left anterior descending coronary artery provoked salvos of ventricular premature complexes and paroxysms of ultrarapid ventricular tachycardia but no ventricular fibrillation in a dog pretreated with procainamide. In the same dog, occlusion without antiarrhythmic therapy resulted in ventricular fibrillation. L = lead.

mature complexes. It may be concluded that patients with malignant ventricular arrhythmias can now be protected from their recurrence.[51]

When Should Ventricular Premature Complexes Be Treated?

So far we have considered the patient with a pronounced predisposition to malignant arrhythmia who was fortunate enough to be resuscitated from one or more such episodes. At present there is no ready method for identifying the patient with an enhanced susceptibility for ventricular fibrillation except retrospectively or when certain advanced grades of ventricular premature complexes have been exposed. It should be emphasized that in the vast majority of patients, ventricular premature complexes require no treatment at all other than the physician's affirmation of their ubiquity and benignity. Therapy is needed in only a minority of patients, who usually have ischemic heart disease and a life-threatening or symptomatically disabling arrhythmia.

With increasing frequency, physicians encounter patients who have been resuscitated from ventricular fibrillation. These patients are at high risk for recurring cardiac arrest, especially if the initial episode was not the direct consequence of acute myocardial infarction. Schaffer and Cobb[21] found that the chance for a repeated episode that may prove lethal was 26 percent during a year of follow-up and that the median time between the first and second bouts of ventricular fibrillation was only 20 weeks.

It is our view that the following other groups need therapy (Table IV): (1) Patients with grade 4 or 5 ventricular premature complexes within the first 6 months after an acute myocardial infarction; (2) patients with profound S-T segment depression and repetitive ventricular premature complexes associated with exercise testing or with complexes exhibiting the R on T phenomenon that are provoked during peak exercise or in the immediate postexercise period; (3) patients with overt evidence of coronary heart disease, especially of recent onset, who have accelerating salvos of ventricular tachycardia during monitoring or exercise; (4) patients with ventricular arrhythmia during an anginal episode; and (5) patients with a prolonged Q-T syndrome associated with frequent ventricular ectopic activity, especially if the patient has a history of syncopal or presyncopal attacks. In all of these patients, therapeutic measures are advisable and even mandatory.

Limitation of Ventricular Premature Complexes as Markers for Sudden Cardiac Death

Ventricular premature complexes of advanced grades in a defined population are the only practical identifying markers of increased risk for sudden death available now. However, the physician faces serious limitations in evaluating these complexes. The first and foremost problem is the ubiquity of these complexes even in persons without heart disease. In addition, it is not certain whether the ventricular premature complex represents the trigger for repetitive activity leading to ventricular fibrillation or whether it is merely an innocuous concomitant of 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 ventricular premature complexes and the predisposition to ventricular fibrillation can be demonstrated. Thus when dogs are pretreated with antiarrhythmic drugs and then subjected to acute coronary artery occlusion, they are protected against ventricular fibrillation, even though no substantial reduction may be observed in either the frequency or grade of ectopic activity (Fig. 9). A further problem the clinician faces in using the ventricular premature complex as a marker is the absence of guidelines to the

extent of ectopic beat suppression that is necessary for protection against sudden death. This issue is complicated by the random occurrence and low reproducibility of advanced grades of arrhythmia. In 65 patients with angiographically proved coronary artery disease and ventricular premature complexes on 24 hour monitoring, repetitive arrhythmias were reproducible in only 40 percent of the patients.[42] Thus a more direct indicator of the electrophysiologic lesion that predisposes the myocardium to ventricular fibrillation is needed.

Identification of Electrical Instability

In the Coronary Drug Program Intervention Trial,[39] the presence of ventricular premature complexes in a single entry electrocardiogram identified patients at increased risk for sudden cardiac death. This risk continued during the 3 year follow-up period. Thus one may surmise that already at the inception of the study, the subset of the population fated to die suddenly had electrical instability of the myocardium. How then can this electrophysiologic abnormality be recognized?

Electrophysiologic markers of electrical instability: Electrophysiologists have examined many markers including excitability, automaticity, conduction velocity, dispersion of refractory period and more intimate attributes of the action potential derived from studies of impaled Purkinje and myocardial fibers.[52–56] However, the malperfused area of myocardium is not homogeneous; this is the necessary consequence of many factors, including varying degrees of impaired oxygen and substrate delivery, varying degrees of fiber stretch, unequal accumulation of diverse metabolites, disparities in extent of innervation, and varying pressure gradients resulting from proximity to epicardial and endocardial surfaces. Indeed different electrophysiologic properties have been described in relation to some of these variables.[57,58] Even careful electrocardiographic mapping of the epicardial surface of the human heart at operation may not identify the pathway or predict the origins of many ventricular tachycardias.[59] The clinician needs some broad measure that will provide insight into the predisposition of the ventricular myocardium to repetitive electrical activity. We believe that such a measure is provided by examining the ventricular vulnerable period, the only interval of the cardiac cycle that permits the consistent induction of repetitive self-sustaining depolarization.

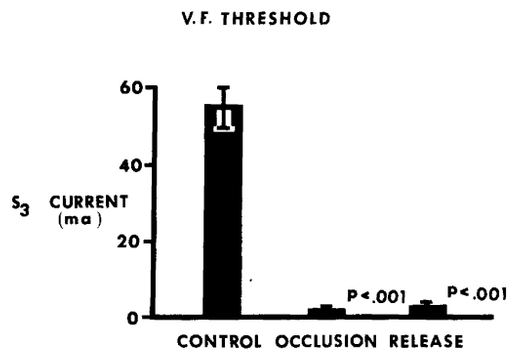

FIGURE 10. The R on T pulsing technique to provoke ventricular fibrillation. Within 2 minutes after the occlusion of the left anterior descending coronary artery in a closed chest dog, the ventricular fibrillation (V.F.) threshold decreased profoundly to triple pulsing (S_3). A similar decrease occurred with reperfusion during release of the occlusion. ma = milliamperes.

TABLE V

Changes in Ventricular Fibrillation Threshold (mean values ± standard error of the mean) in 10 Dogs During 10 Minute Occlusion and Release of the Left Anterior Descending Coronary Artery Measured With Sequential R on T Pulsing[61]

Period of Study	Ventricular Fibrillation Threshold (ma)	Duration of Vulnerable Period (msec)	Duration of Reduced Threshold (min)
Control	56 ± 7.1	14 ± 7	...
Occlusion	1.6 ± 0.3*	76 ± 7*	4.6 ± 0.3
Release	3.6 ± 1.8*	26 ± 7	2.1 ± 0.4

* Differs significantly from the control value ($P < 0.001$ determined with Student's t test).

The ventricular vulnerable period and susceptibility to ventricular fibrillation: In both normal and diseased hearts, a single electrical stimulus causes only a single response. However, markedly suprathreshold stimuli discharged during the brief vulnerable period of the cardiac cycle are required to induce repetitive responses and ventricular fibrillation. This is true even in the presence of acute myocardial ischemia. How then can near-threshold currents induce repetitive electrical activity? We found that when three successive early stimuli are used, the so-called R on T pulsing technique, small physiologic currents suffice to provoke ventricular fibrillation in the animal with ischemic myocardium.[60,61] Two minutes after the left anterior descending coronary artery is abruptly occluded in the closed chest dog, sequential R on T pulsing demonstrates a striking decrease in the ventricular fibrillation threshold and an increase in the length of the vulnerable period (Fig. 10, Table V). This change is transient; within 4 1/2 minutes the threshold returns to pre-occlusion levels. Smaller and briefer alterations in cardiac vulnerability follow reperfusion with abrupt release of the 10 minute occlusion. The time course of these changes in cardiac vulnerability and the altered susceptibility to ventricular fibrillation run parallel to the emergence and recession of arrhythmias after occlusion and release of the coronary artery.

Provocation of repetitive extrasystoles as an indication of reduced threshold to ventricular fibrillation: Such probing with an end point of ventricular fibrillation cannot be used in man; a more innocuous marker is required. We found that the evocation of a dual or multiple response to a single stimulus discharged in the ventricular vulnerable period is a sensitive index of susceptibility to ventricular fibrillation.[62] The awake animal is not aware of the delivery of such stimuli. Repetitive extrasystoles occur reproducibly when 66 percent of the fibrillatory current is administered. The nadir of the repetitive extrasystole threshold

in the cardiac cycle coincides with the vulnerable period for ventricular fibrillation during various maneuvers that alter cardiac vulnerability (Fig. 11).

But how can the repetitive extrasystole be exposed without invasive intracardiac catheterization? We tested mechanical precordial thumping to expose electrical instability in animals.[63] The mechanical stimulus was effective because it depolarized myocardial fibers by transduction of the mechanical pulse into an electrical depolarization[64,65] (Fig. 12). The heart responds as a mechanoelectrical transducer. With sequential R on T pulsing, the provocation of repetitive extrasystoles can be used as an indicator of the presence of a reduced ventricular fibrillation threshold. It is not certain whether this approach will prove possible or informative in man; nonetheless, direct and preferably noninvasive approaches for determining the presence of electrical instability require intensive investigation.

Transient Risk Factors (Neurologic and Psychologic) and Sudden Death

To date, research has been focused exclusively on the heart as the seat of the deranged function leading to sudden cardiac death. Another possibility that might be profitably explored is the identification and control of the transient factors that precipitate ventricular fibrillation, including nervous impulses to the heart, which may be critically important.[66] In fact, the focus should be shifted from the heart as target to the brain as trigger. The therapeutic implications are profound. The evidence for neurophysiologic and psychologic factors in the genesis of ventricular fibrillation were recently presented and will be only briefly reviewed.[67]

Neurophysiologic Studies

The stimulation of specific loci in the posterior hypothalamus and in other areas of the brain can provoke a great number of diverse arrhythmias and lower the ventricular fibrillation threshold. In animals with acute coronary occlusion, such stimuli suffice to provoke ventricular fibrillation. Vagal neural traffic and adrenal catecholamine release are not essential conduits for this brain-heart linkage. Accompanying increases in heart

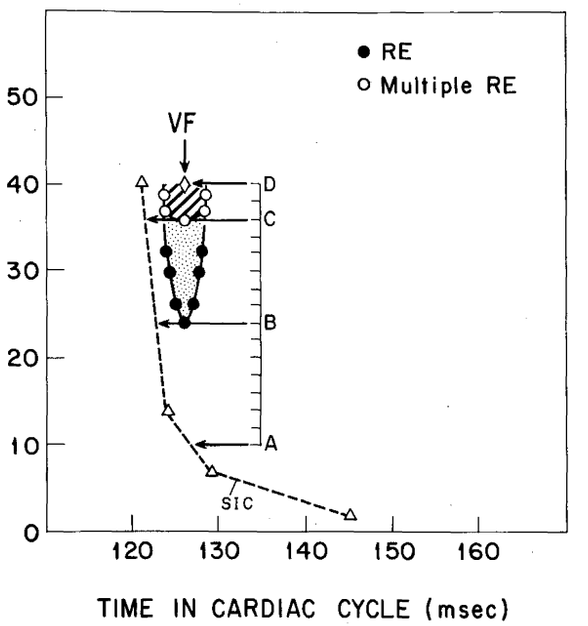

FIGURE 11. Repetitive extrasystole (RE) and ventricular fibrillation (VF) threshold relations determined by scanning the vulnerable period with a 2 msec constant current cathodal stimulus. Electrical diastole was scanned at 1 msec decrements beginning 10 msec after the T wave and ending at the border of strength interval curve (SIC) **(dashed line)**. The ordinate represents the intensity of the stimulus (in milliamperes [ma]), which was increased by 2 ma steps. Repetitive extrasystole current was consistently 66 percent of ventricular fibrillation current; multiple repetitive extrasystole current was 82 percent. (Reprinted from Matta et al., with permission of the publisher.)[62]

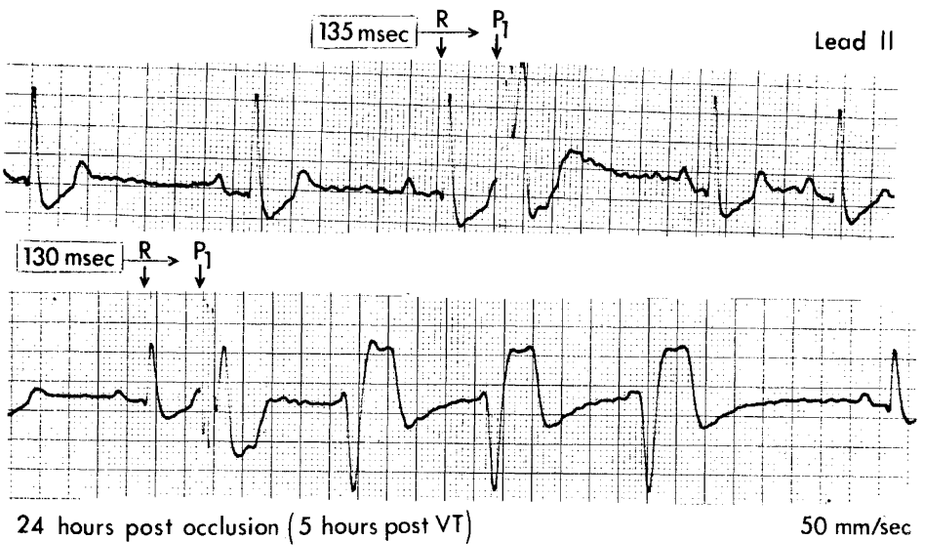

FIGURE 12. A single mechanical pulse (P_1) of chest wall in an awake dog 135 msec after the preceding QRS complex evokes only a single response **(upper tracing)**. However, when the mechanical pulse is delivered 5 msec earlier (130 msec), ventricular tachycardia was consistently induced. When the thump was administered even earlier, ventricular fibrillation occurred in this animal, which had recovered 5 hours earlier from ventricular tachycardia (VT) resulting from occlusion of the left anterior descending coronary artery that had been induced in the preceding 24 hours.

rate and blood pressure are not prerequisites for changes in cardiac excitability. Similar effects can be demonstrated with the stimulation of stellate ganglia, way stations in sympathetic neural connection from the brain to the heart.

Stellate ganglia stimulation: When the stellate ganglia were stimulated, Verrier et al.[68] noted that R on T pulsing of the right ventricle with twice threshold currents provoked ventricular fibrillation in 60 percent of the animals studied. When these ganglia were not stimulated, such pulsing never induced ventricular fibrillation. Schwartz et al.[69–71] provided strong evidence that the left stellate ganglion is dominant in enhancing cardiac vulnerability to fibrillation. These workers also demonstrated that unilateral blockage of the right and left stellate ganglia exert opposite effects on the incidence of arrhythmias associated with myocardial ischemia.[70] The incidence of arrhythmias increased with right blockade but decreased with left blockade. Similar effects were demonstrated on ventricular excitability and cardiac vulnerability to fibrillation.[71] It has long been recognized that the right and left ganglia differ in their effects on the heart. The left stellate mainly affects the posterior ventricular surface, whereas the right ganglion mainly affects the anterior ventricular wall.[72] Left-sided stellate stimulation produces only inotropic effects, whereas right-sided stimulation produces both chronotropic and inotropic changes.[73] Left- and right-sided stellate activation exert reciprocal effects on the S-T segment and T wave as measured with local electrograms. Stimulation of the left or ablation of the right stellate ganglion in dogs results in prolongation of the Q-T interval. No such change occurs when the left stellate ganglion is ablated or the right ganglion is stimulated.[70] However, a predisposition to ventricular fibrillation can be demonstrated when either ganglion is stimulated.

The reflex decrease in sympathetic tone achieved by increasing blood pressure with the injection of the alpha adrenergic stimulating drug, phenylephrine, demonstrated a reduced predisposition to ventricular fibrillation.[74] A protective effect resulting from an increase in blood pressure was also observed during acute myocardial ischemia in the dog.[75]

Sympathetic-parasympathetic interactions: Considerable evidence indicates that the parasympathetic nervous system directly affects the inotropic and chronotropic properties of the ventricle.[76] Recently, Kent et al.[77] demonstrated in open chest dogs that vagal stimulation increased the vulnerable period threshold and protected the acutely ischemic heart against arrhythmia. However, when intact rather than open chest animals were studied, no salutary effects could be attributed to the vagus nerve.[8] With decreased sympathetic discharge, intense vagal stimulation had only slight effects on ventricular vulnerability. However, when sympathetic activity was enhanced by thoracotomy or by direct stimulation of cardiac sympathetic fibers, a definite antifibrillatory vagal effect was observed. After beta adrenergic blockade with propranolol, vagal stimulation did not influence the fibrillation threshold in either open or closed chest dogs. These findings indicate that vagal stimulation has indirect effects that oppose the influence of heightened adrenergic tone on ventricular vulnerability. Kolman et al.[79] reported a similar relation between vagal sympathetic interactions on ventricular excitability.

The effects of the vagus nerve in opposing the vulnerability changes induced by sympathetic neural discharge apply equally to humoral adrenergic release. In their experiments Rabinowitz et al.[80] maintained a constant systemic blood pressure using controlled exsanguination and a fixed heart rate using pacing. However, the injection of norepinephrine markedly decreased the vulnerable period threshold; vagal stimulation restored the threshold to control level but no higher. This action of the vagus nerve on cardiac vulnerability is related to its muscarinic properties and can be annulled by atropine.

In the intact animal, vagal tone adapts to alterations in sympathetic discharge and thereby modulates cardiac vulnerability. Unilateral or bilateral stellectomy, which raises the ventricular fibrillation threshold, had no effect in dogs with intact vagi.[81] Left or right cervical vagotomy decreased cardiac vulnerability and was unaffected by atropine. One may conclude that (1) tonic afferent vagal activity increases the ventricular vulnerability threshold; (2) this effect is mediated by a reflex inhibition of sympathetic outflow by sensory fibers in the parasympathetic trunk; and (3) the protective effect of stellectomy is evident only when the tonic inhibitory influence of afferent vagal activity is removed.[81] The principal locus of vagal projection to the ventricular myocardium is the His-Purkinje system,[82] which also contains many sympathetic neural effector terminals. This system provides the anatomic substrate for sympathetic-parasympathetic interactions on ventricular excitability. There is also evidence of such interaction at the molecular level.[83,84]

The clinical applications of these insights into vagal-sympathetic interactions have led to the use of digitalis glycosides for the control of ventricular premature complexes.[50] We believe that the mechanism accounting for the salutary action of digitalis drugs on ventricular arrhythmias is due to the enhancement of the vagus nerve effect. It has long been known that even small doses of digitalis in man increase carotid sinus sensitivity and thereby augment vagal action.[85] As discussed earlier, the parasympathetic nervous system affects electrical properties of the ventricular myocardium. Therefore it is relevant that parasympathetic maneuvers in man,[86–91] in the form of carotid sinus massage[87,88,91] or the administration of vagomimetic agents,[86,89–91] decrease the frequency of ventricular premature complexes and abolish ventricular tachycardia.

Psychologic Factors and Ventricular Fibrillation

An essential question is whether inputs from higher nervous centers in the brain that mediate biobehavioral changes can affect cardiac vulnerability. More specifically, do psychologic stresses enhance cardiac suscep-

tibility to ventricular fibrillation? To examine this question, we used mild conditioning stresses in awake animals with the repetitive extrasystole threshold as a measure of the ventricular vulnerable threshold.[92] Dogs were exposed to two environments for 3 days: a cage in which the animal was left largely undisturbed, and a Pavlovian sling in which the animal received a single 5 joule transthoracic shock at the end of each experimental period. The two environments were compared on days 4 and 5. At these times, the dogs in the sling were restless, salivated excessively, exhibited somatic tremor and had sinus tachycardia. In the cage, the current that elicited repetitive extrasystoles was 43 ± 5 milliamperes (ma) (mean ± standard error of the mean); in the sling, the mean threshold was reduced to 14 ± 6 ma ($P < 0.001$) (Fig. 13). During testing, heart rates were kept constant with cardiac pacing. The animals with the highest nonpaced heart rates in the sling also had the greatest decrease in threshold for repetitive extrasystoles. These findings indicate that psychologic stress can profoundly lower the cardiac threshold for ventricular fibrillation.

The type of psychologic stress was not critical; thus, when dogs were trained instrumentally to avoid electric shock, this aversive environment also decreased the repetitive extrasystole threshold by 50 percent.[93] Tolamolol hydrochloride, a cardiospecific beta adrenergic blocking drug, prevented the stress-induced alteration of cardiac vulnerability, indicating that the decrease in threshold was mediated by the sympathetic nervous system.

After exposure to the sling environment, the animal recognized it as stressful for a prolonged period even when no longer subjected to any aversive stimuli. When such a conditioned animal recovered from myocardial infarction, merely placing it in the sling provoked ventricular tachyarrhythmia.[94] The nonstressful cage environment did not provoke this response. In recent experiments we found a striking difference in the occurrence of ventricular fibrillation when a coronary artery

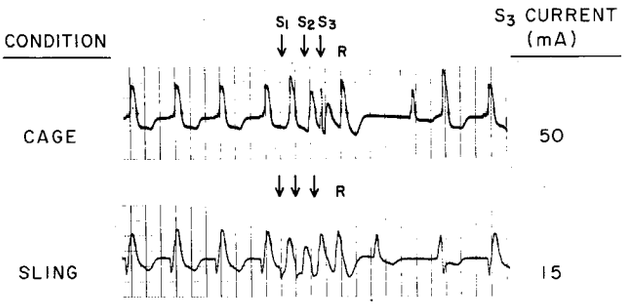

FIGURE 13. The effect of stress conditioning. When the dog was kept in a nonaversive cage environment, the S_3 current in sequential R on T pulsing for eliciting repetitive extrasystoles (R) remained constant at 50 milliamperes (mA). When the animal was transferred to an aversive sling environment, the repetitive extrasystole threshold decreased to 15 mA.

was occluded in the cage or sling environment (Fig. 14).

Neuropharmacologic Investigations

How can neural traffic to the heart be altered, thereby providing protection against ventricular fibrillation? Clonidine was recently demonstrated to decrease vulnerability to ventricular fibrillation in normal canine hearts but not in the hearts of dogs with acute myocardial infarction.[95] The protective effect was associated with a decrease in heart rate and blood pressure, suggesting a general decrease in activity in the efferent limb of the sympathetic nervous system. Ventricular vulnerability to fibrillation was also blunted in an aversive environment using morphine sulfate.[96] Cholinergic blockade of vagal efferent activity with atropine partially annulled the protective action of morphine.

Serotonin precursor to affect ventricular vulnerability: A promising method for affecting ventricular vulnerability involves the inhibition of sympathetic neural traffic by administering serotonin precursors

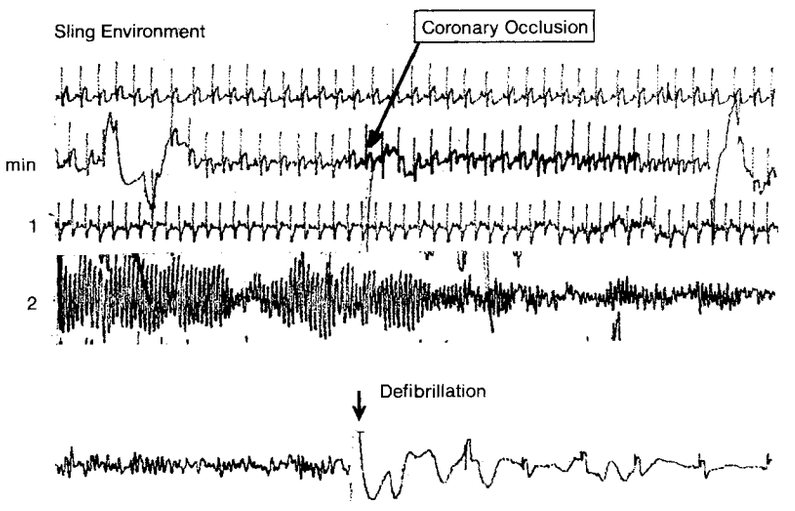

FIGURE 14. Coronary occlusion while the animal was in a sling environment resulted within 2 minutes in ventricular fibrillation. Note the instability of the baseline due to restlessness when the animal was merely standing quietly. When coronary occlusion was carried out while the animal was in the nonaversive cage environment, ventricular fibrillation did not occur.

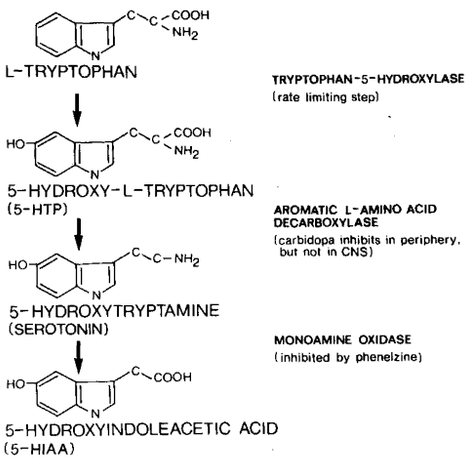

FIGURE 15. The sequence of tryptophan transformation to serotonin and degradation to 5-hydroxyindoleacetic acid (5-HIAA). Carbidopa inhibits decarboxylation of 5-hydroxy-L-tryptophan and prevents the formation of serotonin in the periphery but does not cross the blood-brain barrier, whereas phenelzine inhibits monoamine oxidase and prevents the metabolism of serotonin, thus causing its accumulation in the central nervous system (CNS).

that localize in the central nervous system.[97–99] Rabinowitz and Lown[100] examined whether manipulation of serotinin in the central nervous system can affect cardiac vulnerability. Dogs were injected with serotonin precursors, L-tryptophan or 5-hydroxy-L-tryptophan, in conjunction with the monoamine oxidase inhibitor phenelzine and the selective peripheral L-amino acid decarboxylase inhibitor carbidopa. Tryptophan is an essential dietary amino acid and 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. This sequence is altered in two important ways by phenelzine and carbidopa (Fig. 15). Phenelzine inhibits monoamine oxidase so that serotonin tends to accumulate wherever it forms. 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 serotonin precursor is selectively diminished peripherally and therefore largely restricted within the central nervous system. One would therefore expect that the administration of tryptophan or 5-hydroxy-tryptophan to animals pretreated with phenelzine and carbidopa would result in the formation of serotonin and its accumulation within the central nervous system but not in the periphery.

In these animals, ventricular vulnerability was evaluated by measuring the repetitive extrasystole threshold. A sustained increase of 50 percent in the repetitive extrasystole threshold resulted only when the biochemical measures that presumably increase serotonin in the central nervous system were used. Thus, neuropharmacologic measures affecting central sympathetic activity alter cardiac vulnerability and may protect against ventricular fibrillation.

Clinical Implications

In man and in the experimental animal, neural and psychologic factors predispose to ventricular arrhythmias and may precipitate sudden cardiac death.[101,102] The decrease in sympathetic neural activity during sleep is associated with a decrease in the frequency and grade of ventricular premature complexes.[103] Psychologic stress in predisposed individuals can increase the frequency of ventricular ectopic activity and was even associated with the triggering of ventricular fibrillation.[104,105] Beta adrenergic blocking drugs decreased the incidence of sudden death in patients with myocardial infarction.[106]

Defining the possible is a critical touch stone of progress. Resolution of the problem of sudden cardiac death has now become a realizable scientific objective. The prerequisites for the achievement of this goal include the development of noninvasive screening methods to determine the presence of cardiac electrical instability, the introduction of safe and long-acting antiarrhythmic drugs that protect against ventricular fibrillation and the discovery of methods to interdict higher neural activity that can destabilize heart rhythm.

Medical history teaches that the consequences of a disease are frequently controlled before its underlying mechanisms are fully understood. In medicine, great rewards have flowed from partial answers and usually have preceded complete solutions. This is the case with sudden cardiac death. The physician is not unmindful of the ultimate futility, but although there is no cure for sudden death there is high art in its deferment.

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