Neural and Psychologic Mechanisms and the Problem of Sudden Cardiac Death

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Brain stimulation can provoke a variety of arrhythmias and lower the ventricular vulnerable threshold. In the animal with acute myocardial ischemia such stimuli suffice to provoke ventricular fibrillation. Vagal neural traffic or adrenal catecholamines are not the conduits for this brain-heart linkage. Accompanying increases in heart rate or blood pressure are not prerequisites for the changes in cardiac excitability. Increased sympathetic activity, whether induced by neural or neurohumoral action, predisposes the heart to ventricular fibrillation. Protection can be achieved with surgical and pharmacologic denervation or reflex reduction in sympathetic tone. With acute myocardial ischemia, augmented sympathetic activity accounts for the early surge of ectopic activity frequently precipitating ventricular fibrillation. Asymmetries in sympathetic neural discharge may also contribute to the genesis of serious arrhythmias. The vagus nerve, through its muscarinic action, exerts an indirect effect on cardiac vulnerability, the consequence of annulment of concomitant adrenergic influence, rather than of any direct cholinergic action on the ventricles. There exist anatomic, physiologic as well as molecular bases for such interactions. Available experimental evidence indicates that environmental stresses of diverse types can injure the heart, lower the threshold of cardiac vulnerability to ventricular fibrillation and, in the animal with coronary occlusion, provoke potentially malignant ventricular arrhythmias. Available evidence indicates that in man, as in the experimental animal, administration of catecholamines can induce ventricular arrhythmia, whereas vagal activity exerts an opposite effect. Furthermore, in certain subjects diverse stresses and various psychologic states provoke ventricular ectopic activity.

To identify and protect the subject at risk from sudden death presents a significant challenge in contemporary cardiology. Were such death but the end stage of irreversible atherosclerosis, this would be a futile endeavor, but experience in the coronary care unit sanctions a different conclusion. It has repeatedly been demonstrated that sudden death is not the relentless culmination of far advanced coronary disease incompatible with survival. In fact, it is the result of ventricular fibrillation that can readily be reversed and, once reversed, is unlikely to recur. The near fatal event can be viewed as an electrical accident most frequently induced by acute myocardial ischemia. If an effective therapeutic strategy is to be developed, clear conceptualization of this problem is required.[1-3] Four interrelated hypotheses are central to this conception:

1. The mechanism of sudden death is ventricular fibrillation.
2. Electrical instability of the myocardium may long precede onset of the catastrophic arrhythmia.
3. Certain types of ventricular premature beats may reflect the presence of electrical instability, and their occurrence in the electrically unstable heart may predispose to repetitive ventricular activity leading to ventricular fibrillation.
4. Transient risk factors induce electrical instability and in the electrically unstable heart can increase cardiac susceptibility to ventricular fibrillation. Generally these transient risk factors derive from higher nervous activity.

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This last hypothesis requires close examination. If nervous impulses are indeed critical to the problem of sudden death, newer methodologic approaches for identifying threatened subjects are both necessary and possible. There are also profound therapeutic implications wherein the focus shifts from the heart as target to the brain as trigger. We shall first consider animal models and then assess the problem in man.

Animal Models

Central Nervous Stimulation and Cardiac Arrhythmias

Sixty years ago, Levy[4,5] clearly demonstrated that injection of drugs such as nicotine, barium chloride or epinephrine into certain areas of the brain in cats anesthetized with chloroform produced ventricular extrasystoles and occasionally ventricular fibrillation. These findings, subsequently confirmed in a variety of species,[6–10] were extended to other chemicals including acetylcholine,[7,8] caffeine[8] and strophanthidin,[10] which were injected into various cortical and midbrain structures. Imprecision of localization and the unphysiologic concentration of injectates made determination of the loci responsible for arrhythmias uncertain. A preferable approach involved the delivery of small electrical stimuli by means of unipolar or bipolar electrodes stereotaxically positioned into various sites in the brain. Studies involving cortical stimulation have been comprehensively reviewed by Delgado[11] and by Hoff et al.[12] Cortical areas affecting cardiovascular function include the upper portion of the frontal lobe, the orbital cortex, the motor and premotor cortex, the hidden motor areas, the anterior part of the temporal lobe, the insula and cingulate gyrus. Electrical stimulation of these areas modifies heart rate and blood pressure and may induce atrial and ventricular extrasystoles. Arrhythmias are more readily provoked from subcortical structures.[13] Stimulation of the thalamus and basal ganglia has little effect on heart rate, arterial pressure or heart rhythm. However, the hypothalamus serves as an important cardiac neuroregulatory center transmitting impulses by way of the reticular formation to the heart. Although stimulation of the anterior hypothalamus induces bradycardia and hypotension, ventricular rhythm is unaffected.[13] In contrast, stimulation of the posterior hypothalamus produces little or no cardiac acceleration but results in prompt and profound systemic hypertension. Ventricular extrasystoles occasionally emerge, but these are more frequent after cessation of stimulation. Korteweg et al.[13] concluded that the most important subcortical regions involved in the regulation of cardiac rhythm are located in the hypothalamus and quadrigeminal bodies.

Ventricular fibrillation: In the normal heart, ventricular fibrillation generally does not follow central nervous system stimulation although a diversity of arrhythmias such as atrial, junctional and ventricular mechanisms have been recorded. Garvey and Melville[14] carried out hypothalamic stimulation after two stage coronary arterial ligation. In three of four animals fatal ventricular fibrillation developed within 10 to 60 seconds after hypothalamic stimulation carried out within 20 to 30 hours after coronary occlusion. These findings are not persuasive because two of five control animals without coronary occlusion also experienced ventricular fibrillation. Furthermore, in a second experiment replicating the conditions of the first study, ventricular fibrillation could not be produced.[15]

The greatest predisposition to ventricular fibrillation is at the inception of myocardial ischemia; it seemed relevant therefore to examine whether hypothalamic stimulation would precipitate ventricular fibrillation in the animal exhibiting extreme electrical instability. Satinsky et al.[16] examined this question in dogs. In 16 normal dogs, hypothalamic stimulation failed to induce ventricular arrhythmias. Two 10 minute occlusions were then induced with an intervening recovery period of 40 minutes. Hypothalamic stimulation was randomized. For each experiment involving such central nervous stimulation, two control occlusions were accomplished. In the absence of hypothalamic stimulation, during 32 coronary arterial ligations, only two episodes (6.3 percent) of ventricular fibrillation were observed. After 1 minute of posterior hypothalamic stimulation, 10 of 16 dogs (62.5 percent) with coronary occlusion manifested ventricular fibrillation (Table I).

The precise mechanisms whereby central nervous system activation alters myocardial susceptibility to ventricular fibrillation remain uncertain. The early experiments of Beattie et al.[6] on neural degeneration indicated that sympathetic pathways emanating from the hypothalamus were implicated in the genesis of ventricular arrhythmia. These findings have been supported by more recent data.[17,18] The susceptibility to ventricular ectopy associated with stimulation of various cortical and subcortical structures[11–13] is prevented by cardiac sympathectomy[19] or beta adrenergic blockade.[17,18] Parasympathetic pathways are probably not involved because bilateral vagotomy leaves unaltered the arrhythmogenic effect of central nervous system stimulation[13,14,17,18] (Fig. 1). The ventricular arrhythmias that immediately follow cessation of diencephalic stimulation require intact vagi and stellate ganglia.[13,19]

Before one accepts the thesis that hypothalamic activity may precipitate ventricular fibrillation by direct sympathetic nervous traffic to the heart, several variables need to be controlled.[18] Hypothalamic stimulation is accompanied by substantial hemodynamic alterations that may contribute to arrhythmogenesis. The heart rate accelerates by an average of 85 beats/min, and systolic and diastolic pressures increase by 55 and 45 mm Hg, respectively. The lowering in ventricular fi-

TABLE I. Occurrence of Ventricular Fibrillation (VF) During Posterior Hypothalamic Stimulation With and Without Coronary Ligation

Coronary Ligation	Hypothalamic Stimulation			
	no.	No VF	no.	VF
No	0	0	16	0
Yes	32	2 (6.3%)	16	10* (62.5%)

*$P < 0.005$.

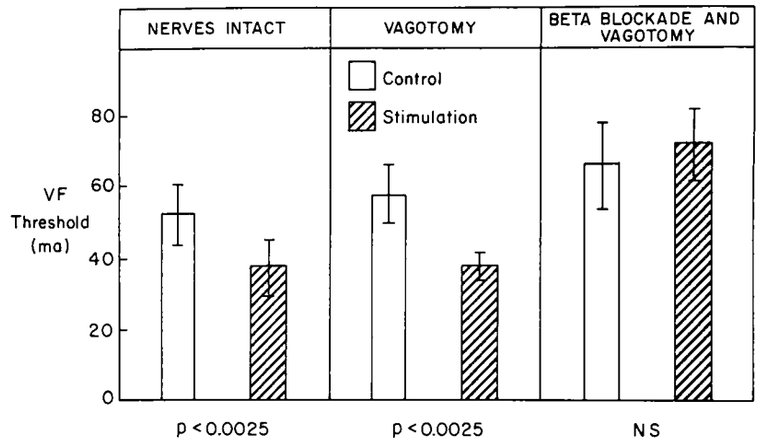

FIGURE 1. Effect of vagotomy and beta adrenergic blockade (propranolol, 0.25 mg/kg body weight) on reduction in ventricular fibrillation (VF) threshold associated with posterior hypothalamic stimulation. The decrease in threshold during hypothalamic stimulation is not affected by bilateral cervical vagotomy (**middle panel**) but is completely abolished with beta blockade (**right panel**). NS = not significant; p = probability. (Reproduced from Verrier et al.[18] with the permission of the publisher.)

brillation threshold after hypothalamic stimulation persists in animals with complete heart block. The evoked pressor effect similarly does not contribute to the observed changes; when an increase in blood pressure is precluded by controlled exsanguination, the same reduction in ventricular fibrillation threshold is observed after hypothalamic stimulation. Release of adrenal medullary catecholamines appears not to be the critical factor because adrenalectomy does not alter the changes in cardiac vulnerability after hypothalamic stimulation. No effect can be ascribed to the vagus, since bilateral vagotomy does not annul the observed changes.

Thus, brain stimulation can provoke a variety of arrhythmias and lower the ventricular vulnerable threshold. In the animal with acute myocardial ischemia such stimuli suffice to provoke ventricular fibrillation. Vagal neural traffic or adrenal catecholamines are not the conduits for this brain-heart linkage. Accompanying increases in heart rate or blood pressure are not prerequisites for the changes in cardiac excitability.

A major limitation of investigations dependent upon the use of large electrical currents for stimulating the brain is that activation of adjoining neural structures no doubt occurs, resulting in complex and unpredictable sequelae.[11,22] Furthermore it remains speculative whether responses elicited by such artifactual devices are not epiphenomena without physiologic counterparts.

Peripheral Sympathetic Nervous System and Ventricular Fibrillation

There is substantial evidence suggesting that enhanced sympathetic nervous system activity predisposes to ventricular fibrillation.[20–24] In normal laboratory animals, electrical stimulation of cardiac sympathetic fibers markedly lowers the vulnerable period threshold[20,22,23] and in the presence of myocardial ischemia results in ventricular fibrillation.[21] According to Schwartz et al.,[25,26] the left stellate ganglion is dominant in this respect. It has long been recognized that the right and left ganglia differ in their cardiac effects.[27–29] The left stellate exerts its influence predominantly on the posterior ventricular surface, whereas the right ganglion affects mainly the anterior ventricular wall.[29] Left-sided stellate stimulation produces exclusively inotropic effects, whereas right-sided stimulation results in both chronotropic and inotropic changes.[28] 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.[27,29]

Our current investigations indicate a 37 percent lowering in the ventricular fibrillation threshold when the left ganglion is stimulated compared with a 21 percent reduction when stimulation is carried out on the right side[30] (Table II). As with hypothalamic stimulation, prevention of cardiac acceleration and the pressor effect does not obtund the sympathetic nervous changes in cardiac vulnerability.[22] However, when efferent fibers from the stellate ganglion are sectioned or when the animals are pretreated with beta adrenergic blocking drugs, the alterations in cardiac vulnerability after sympathetic stimulation are completely prevented.[22] These findings indicate that the predisposition to ventricular fibrillation associated with increased sympathetic nervous activity results from the direct action of norepinephrine released at localized myocardial sites.

Effect of catecholamines: The influence of medullary catecholamines on cardiac excitable properties appears to be considerably less than that exerted by neural input to the heart. Direct stimulation of the nerve supply to the adrenal gland produced only a moderate effect on ventricular automaticity compared with that observed during stellate ganglion stimulation.[31] Han et al.[20] found that infusion of catecholamines produced only a moderate and transient reduction in the fibrillation threshold. However, we have recently demonstrated that when subpressor doses of norepinephrine are given or when the pressor response to large doses of the drug is controlled by exsanguination, norepinephrine produces a significant and sustained reduction in vulnerable period threshold.[32,33]

Sympathectomy: A protective effect of cardiac sympathectomy against ventricular fibrillation in dogs after coronary arterial occlusion was demonstrated more than 40 years ago by Leriche et al.[34,35] Their findings have been corroborated by many investigators.[26,36–38] Total cardiac denervation prevents the emergence of ventricular tachycardia and reduces the occurrence of ventricular premature beats after acute coronary occlusion in awake dogs.[37] The incidence of ventricular fibrillation is reduced from 52 to 0 percent in dogs subjected to mediastinal neural ablation.[38] Bilateral stellectomy substantially raises the ventricular fibrillation threshold in the normal animal.[23] Of special interest is the finding of Schwartz et al.[25] that the two stellate ganglia exert opposite effects on cardiac vulnerability. With either ablation or cooling of the left stellate ganglion, ventricular fibrillation threshold increased by 72 percent compared with control values. By contrast, similar treatment of the right side lowered the threshold by 48 percent compared with the control value. The basis for the paradoxic effect of right stellectomy was elucidated in a recent collaborative study by Schwartz et al.[39] It was found that the increase in ventricular excitability associated with unilateral right stellectomy was mediated by compensatory reflex activation of the dominant left stellate ganglion. Thus the direct effect of the right ganglion in decreasing excitability was masked by the increase in excitability produced by reflex activation in the left ganglion. That imbalance in neural activity may play a role is supported by the investigations of Randall et al.[40] Total denervation of the canine heart, while sparing the ventrolateral cardiac nerve, resulted in a model of sympathetic nervous cardiac imbalance. Direct electric stimulation of this nerve or exercise stress induced diverse arrhythmias including ventricular tachycardia.

The response pattern to stellectomy or sympathetic denervation appears to be more complex because when vagi are intact or there is efferent vagal blockade with atropine, unilateral or bilateral stellectomy does not alter the vulnerable period threshold for ventricular fibrillation[30,41] (Fig. 2). This finding suggests that vagus nerve afferent traffic modulates sympathetic tone and in the resting animal maintains it at a low level. A similar reflex phenomenon is observed during acute increases in blood pressure after alpha-adrenergic stimulation or clamping of the thoracic aorta. Such baroreceptor activation results in a rise in fibrillation threshold. The protection against ventricular fibrillation is due to withdrawal of sympathetic nervous output, which can be abolished with baroreceptor denervation or beta adrenergic blockade.[32] This is consistent with the nerve recording studies from several laboratories[42–44] showing that afferent activity in the vagi maintains sympathetic outflow at a reduced level.

TABLE II

Comparison of Effect of Left and Right Stellate Ganglion Stimulation on Repetitive Extrasystole Threshold (ma)

	Left	Right
Control	24 ± 2 (P <0.001)	23 ± 2 (P <0.004)
Stimulation	15 ± 1	18 ± 2

Values are means ± standard error of the mean.

Sympathetic activity during myocardial ischemia: Because arrhythmias are most ubiquitous during myocardial ischemia, it is worth considering briefly the interplay of adrenergic neural factors. Brown[45] and Malliani et al.[46] demonstrated that a sympathetic cardiocardiac reflex is elicited by acute coronary occlusion. Within 1 minute of coronary arterial obstruction in the cat, there was a surge in the firing rate of cardiac-bound sympathetic fibers, which was mediated by a spinal reflex. Gillis[47] obtained comparable results. Kelliher et al.[48] showed that the secretion rate of epinephrine increases up to eightfold within the first 2 minutes of acute coronary ligation. The increased release of catecholamines has been shown by Staszewska-Barczak[49] to be mediated reflexly by vagal as well as extravagal pathways and supraspinal structures.

The time course of changes in adrenergic tone input to the heart appears to correspond closely with the spontaneous occurrence of ventricular fibrillation and with the reduction in vulnerable-period threshold during coronary occlusion.[50–52] Axelrod et al.[52] showed that within 1 to 2 minutes of obstruction of the left an-

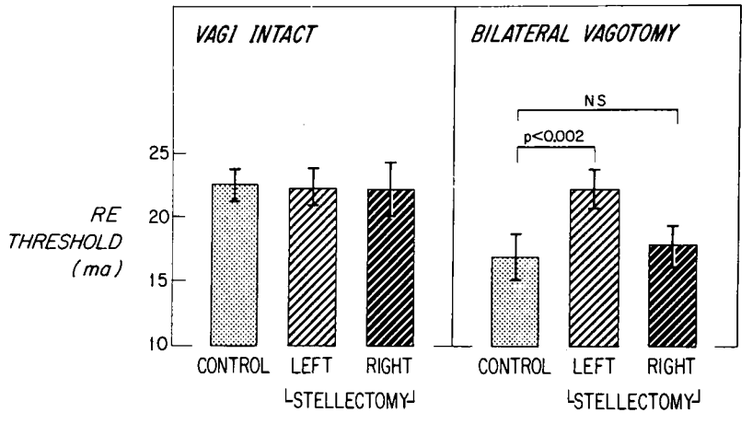

FIGURE 2. Effect of unilateral stellectomy with and without vagotomy on repetitive extrasystole (RE) threshold. When vagi are intact, stellectomy does not alter the vulnerable period threshold. When vagi are sectioned bilaterally, left stellectomy significantly increases the repetitive extrasystole threshold (**right panel**). N.S. = not significant; p = probability.

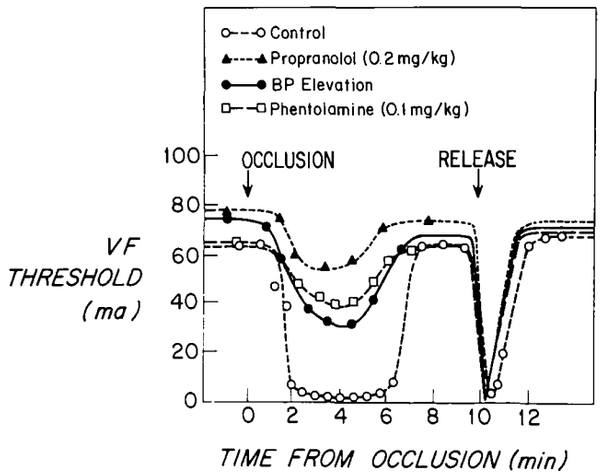

FIGURE 3. Protective effect of decreasing adrenergic input to the heart during a 10 minute period of coronary occlusion followed by abrupt reperfusion. Beta (propranolol, 0.25 mg/kg) and alpha (phentolamine, 0.1 mg/kg) adrenergic blockade and reflexly induced reduction in cardiac sympathetic tone with elevation of blood pressure (BP) affords significant protection against vulnerbility during coronary occlusion. However, these interventions fail to protect against ventricular fibrillation (VF) during reperfusion.

terior descending coronary artery in the dog, there is a profound decrease in the vulnerability threshold so that a current level just sufficient to evoke a propagated response can trigger ventricular fibrillation. This period of enhanced vulnerability persists for 6 to 7 minutes; after this time the fibrillation threshold recovers despite continued occlusion. Upon release of the occlusion after an ischemic period of 10 minutes, reduction in fibrillation threshold occurs within 20 to 30 seconds and persists for less than 1 minute.

Administration of beta adrenergic blocking agents such as propranolol[53] or the cardioselective blocking agent tolamolol[54] affords nearly complete protection against vulnerability associated with occlusion. Alpha adrenergic blockade with phentolamine is also effective against myocardial ischemia-induced enhancement in vulnerability[53,55] but is ineffective during release of coronary occlusion. Reflexly induced reduction in cardiac sympathetic tone by acute blood pressure elevation significantly protects against ventricular fibrillation during coronary occlusion but not during reperfusion[56] (Fig. 3). The salutary effect of an increase in blood pressure can be abolished by baroreceptor denervation. Thus, alterations in neural tone and not improved coronary perfusion are responsible for the beneficial effect of blood pressure elevation. These findings indicate that increased adrenergic input is largely responsible for the susceptibility to ventricular fibrillation during myocardial ischemia but that enhanced cardiac vulnerability during reperfusion is related to other factors.

Thus, increased sympathetic activity, whether induced by neural or neurohumoral action, predisposes the heart to ventricular fibrillation. Protection can be achieved with surgical and pharmacologic denervation or reflex reduction in sympathetic tone. With acute myocardial ischemia, augmented sympathetic activity accounts for the early surge of ectopic activity frequently precipitating ventricular fibrillation. Asymmetries in sympathetic nervous discharge may also contribute to the genesis of serious arrhythmias.

Because sympathetic nervous effects on the heart are not isolated from complex and concurrent alterations in the activity of the parasympathetic nervous system, it is necessary to examine the possible role of the vagus on susceptibility to ventricular fibrillation.

Vagus Nerve Effects

Does vagal innervation extend to the ventricles and is its distribution sufficient to affect myocardial function? A prevailing clinical view is that vagal effects on ventricular myocardium are negligible. Indeed, if a tachycardia responds to cholinergic measures, the site of impulse formation is deemed to be supraventricular. However, considerable evidence has recently been amassed indicating that parasympathetic nervous influences directly affect the inotropic and chronotropic properties of the ventricles.[57] For example, it has been shown that vagal stimulation exerts a distinct negative inotropic effect on the isovolumic canine ventricle.[58,59] Acetylcholine in relatively small concentrations depresses phase 4 of the action potential of in-situ proximal His-Purkinje fibers while augmenting conduction velocity.[60] In dogs with atrioventricular block, stimulation of the vagus nerve depresses ventricular rate.[61] These effects, although measurable, are much smaller than those observed in atrial tissues.[57] These findings are consonant with anatomic evidence of rich cholinergic innervation of atrial tissue and sparse vagal distribution to the ventricular myocardium. However, ventricular conduction tissue is abundantly endowed with cholinergic innervation.[62,63] Thus it might be anticipated that the vagus nerve can modify ventricular electrical stability.

These recent findings are in accord with a century-old observation. In 1859 Einbrodt, a Russian working in Karl Ludwig's laboratory,[64] found that vagal stimulation raised the threshold for ventricular fibrillation in open chest dogs. Kent et al.[62] and Myers et al.[65] confirmed and extended this observation; they showed that vagus stimulation increases the threshold of the vulnerable period in normal as well as ischemic dogs. However, when instead of open chest dogs, intact animals were studied, no salutary effect could be attributed to the vagus.[66]

Sympathetic and parasympathetic interactions: In the basal state in closed chest dogs with rate maintained constant by transvenous pacing, vagus nervous stimulation is without effect on cardiac vulnerability. With adrenergic stimulation, provided either by left stellate ganglion stimulation[66] or catecholamine infusion, substantial vagal effects on cardiac vulnerability are demonstrable.[33] However, the fibrillation threshold is raised only to its control level and, in the animal pretreated with beta adrenergic blocking drugs, vagal induced changes in cardiac vulnerability[66,67] and excitability[68] are completely annulled (Fig. 4). Thus, vagal action is indirect and is expressed by opposing the effects of heightened adrenergic tone[24] (Fig. 5).

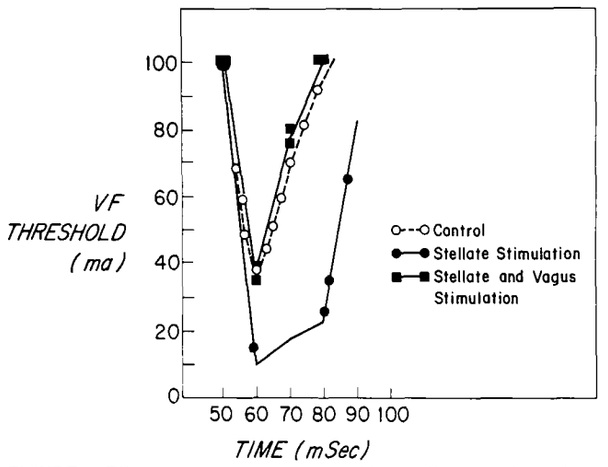

FIGURE 4. Effect of concurrent vagal and left stellate ganglion stimulation on ventricular vulnerability. Stellate stimulation decreases the ventricular fibrillation (VF) threshold and increases the duration of the vulnerable period. Concurrent vagal stimulation completely annuls the effects of sympathetic activation on vulnerability.

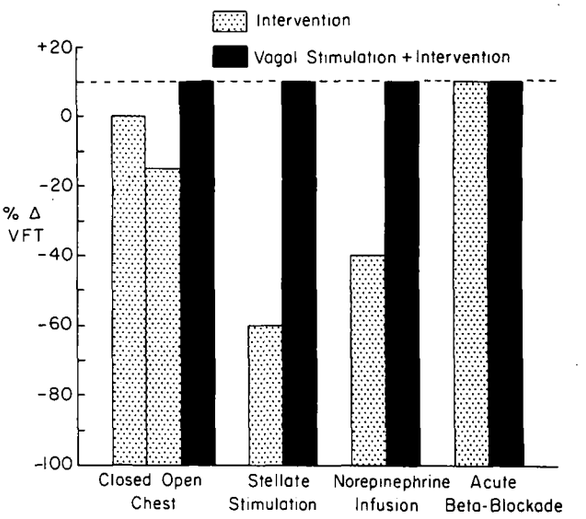

FIGURE 5. Influence of vagal stimulation on ventricular fibrillation threshold (VFT) in the presence of various levels of adrenergic input. An effect of vagal activation is evident only when neural or humoral activity is enhanced. (Reproduced from Lown and Verrier[24] with permission of the publisher.)

The vagus is a mixed nerve, capable of eliciting muscarinic, nicotinic and adrenergic effects. To determine which of its various actions are implicated in its capacity to alter ventricular vulnerability in the sympathetically aroused animal, the muscarinic agent methacholine was infused intravenously. Methacholine raised the vulnerable threshold, which could be restored to the control level with the selectively muscarinolytic agent atropine.[33] Muscarinic agents have been shown to inhibit the release of norepinephrine from sympathetic nerve endings and to attenuate the response to norepinephrine action at receptor sites.[69-72] The vagal antagonism to both neural and humoral sympathetic influences is therefore entirely consistent with its muscarinic properties.[71] The principle locus of vagal projection to the ventricle is the His-Purkinje system,[63] which is also richly endowed with sympathetic neuroeffector terminals. This provides the anatomic substrate for sympathetic-parasympathetic interaction on ventricular excitability. There is also evidence of such interaction at the molecular level. Because catecholamine action is contingent on the synthesis of cyclic adenosine monophosphate (AMP) in many tissues,[73] it is of interest that acetylcholine reduces this synthesis. Murad et al.[74] have found that acetylcholine diminished adenyl cyclase-directed cyclic adenosine-3′,5′-monophosphate (cAMP) synthesis from a variety of broken-cell cardiac tissues and that this reduction was blocked by atropine. LaRaia and Sonnenblick[75] demonstrated that carbamylcholine blockade of cAMP synthesis was associated with a reduction in tension in isolated cat atrial and ventricular muscle strips and that the effect was again abolished with atropine; by contrast, norepinephrine increased cAMP synthesis in parallel with increases in developed tension. In recent studies, Watanabe and Besch[76] more precisely defined the subcellular basis for adrenergic-cholinergic antagonism as possibly being mediated by cyclic AMP-cyclic guanosine monophosphate (GMP) interactions. Acetylcholine was noted to elevate cyclic GMP levels in isolated guinea pig ventricles without altering contractility. These same concentrations of acetylcholine significantly attenuated the inotropic effects of drugs that elevate levels of cyclic AMP. Because the acetylcholine did not decrease generation of cyclic AMP, their evidence suggests that the antiadrenergic effects of acetylcholine were due to antagonism of the inotropic action of cyclic AMP by cyclic GMP.

The vagus nerve, through its muscarinic action, exerts an indirect effect on cardiac vulnerability, the consequence of annulment of concomitant adrenergic influence, rather than of any direct cholinergic action on the ventricles. There exist anatomic, physiologic as well as molecular bases for such interactions.

Psychologic Stresses and Ventricular Fibrillation

Perhaps the most relevant question relating to neural activity and sudden death is whether behavioral and psychologic factors can increase cardiac vulnerability and predispose to ventricular fibrillation. Raab[77] has extensively reviewed the available literature indicating that diverse psychologic stresses may induce myocardial necrosis and infarction in different species. These stresses have involved interference with rats' access to food while exposing them to tape recordings of noisy struggles with cats,[78] "yoked chair" aversive avoidance experiments in monkeys[79] and animal crowding.[77] Subjecting pigs to unavoidable small electric shocks while they are paralyzed with muscle relaxants likewise provokes within 24 hours significant cardiomyopathy.[80] The cardiac lesions are believed to result from a direct deleterious effect of neural and neurohumoral agencies on myocardium because the coronary arteries are free of any discernible pathologic alteration.

Notwithstanding the anatomic evidence of stress-induced myocardial injury, until recently no experi-

mental data were available relating to the effect of psychologic variables on cardiac susceptibility to ventricular fibrillation. This was largely due to the absence of suitable methods for repeatedly determining cardiac vulnerability in the intact unanesthetized animal. Such assessment requires the use of painful test stimuli, induction of ventricular fibrillation and use of traumatic resuscitation procedures that preclude meaningful investigation of psychologic variables. It was necessary to devise an appropriate end point that could serve as an index of vulnerability to ventricular fibrillation.

Before the emergence of ventricular fibrillation, when test stimuli of increasing current are applied to the myocardium, repetitive extrasystoles are evoked. Such multiple responses to a single stimulus occur when 66 percent of the fibrillation current is delivered.[67] The timing in the cardiac cycle of the threshold nadir for repetitive extrasystoles coincides with the vulnerable period for ventricular fibrillation. Moreover, neurohumoral interventions such as stellate and vagal stimulation, norepinephrine infusions and beta adrenergic blockage produce comparable changes in the threshold for repetitive extrasystoles and ventricular fibrillation.[33,66,67] These interventions also result in equivalent shifts in timing of the vulnerable period in the cardiac cycle. Similar alterations occur when autonomic tone is changed with drugs such as phenylephrine, methacholine and morphine sulfate.[24] A consistent relation between repetitive extrasystole and ventricular fibrillation thresholds has also been noted in conscious dogs (DeSilva R, Verrier RL and Lown B, unpublished observation). These observations suggest that repetitive extrasystole and ventricular fibrillation thresholds share a common electrophysiologic basis and that the threshold for repetitive extrasystoles can be utilized as a marker of cardiac vulnerability for ventricular fibrillation.

The repetitive extrasystole end point was therefore used in a recent study of the effects of a simple aversive psychologic paradigm.[81] Dogs were exposed to two different environments: a cage in which the animal was left largely undisturbed; and a Pavlovian sling in which the animal received a single 5 joules transthoracic shock at the end of each experimental period for 3 successive days. The two environments were compared on days 4 and 5. At these times, dogs 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 current that elicited repetitive extrasystoles was 43 ± 5 milliamperes (± standard error of the mean); in the sling, the mean threshold was reduced to 14 ± 6 (P <0.001). During testing, heart rates were held constant by cardiac pacing. The animals with the highest nonpaced heart rates in the sling also had the greatest reduction 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 reduced the repetitive extrasystole threshold by 50 percent. That the lowering in threshold was mediated by the sympathetic nervous system is deduced from the fact that the cardiospecific beta adrenergic blocking drug tolamolol hydrochloride completely prevented the stress-induced alteration of cardiac vulnerability[82] (Fig. 6).

An important question was whether psychologic stress can provoke ventricular arrhythmias in the predisposed animal without requiring external electric stimulation. This question was examined in dogs subjected to coronary occlusion.[83] The animals were conditioned according to the cage-sling paradigm described above. After 5 consecutive days in which they spent 1 hour in the cage and 1 hour in the sling, a balloon occluder, previously implanted around the left anterior descending coronary artery, was inflated. Once the animals had recovered fully from the occlusion and were entirely free of arrhythmia, they were reexposed to the two environments. The sling environment consistently resulted in diverse ventricular arrhythmias including ventricular tachycardia and R on T extrasystoles; these effects disappeared when the animals were returned to the nonaversive cage (Fig. 7). Observations of Skinner et al.[84] are relevant in this context. They found that adaptation of farm pigs to a laboratory environment during a 4 to 8 day period significantly retarded or prevented the onset of ventricular fibrillation associated with coronary occlusion. Surprisingly, however, beta adrenergic blockade with propranolol did not afford any protection against the development of ventricular fibrillation in unadapted animals. Pharmacologic blockade of adrenergic input to the heart and environmental adaptation did not yield equivalent results. It remains to be determined whether the failure of propranolol to protect against ventricular fibrillation was due to inadequate blockade of adrenergic input to the heart or to the involvement of extraadrenergic factors in the antifibrillatory effect of psychologic adaptation.

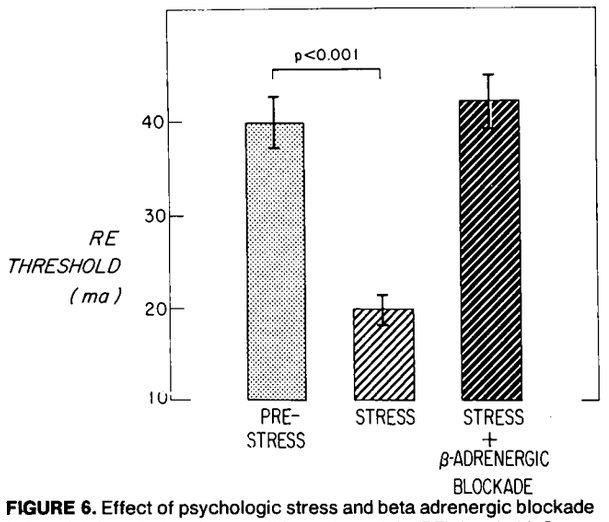

FIGURE 6. Effect of psychologic stress and beta adrenergic blockade (tolamolol 4 mg/kg) on the repetitive extrasystole (RE) threshold. Stress induces a significant decrease in threshold that is prevented by beta blockade.

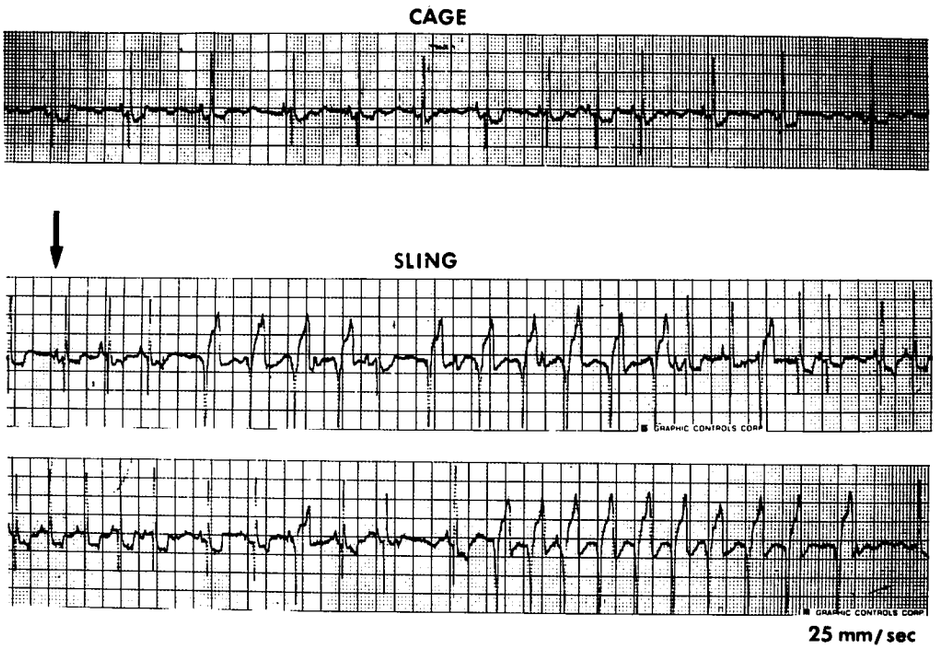

FIGURE 7. Psychologic stress provokes ventricular tachycardia in an animal with previous coronary occlusion. While the animal is in a tranquil cage environment, there is sinus arrhythmia without ventricular ectopic activity. By contrast, when it is in the stressful sling environment there is frequent and sustained ventricular tachycardia.

Available experimental evidence indicates that environmental stresses of diverse types can injure the heart, lower the threshold of cardiac vulnerability to ventricular fibrillation and, in the animal with coronary occlusion, provoke potentially malignant ventricular arrhythmias. The precise neural pathways mediating psychologic inputs to the heart affecting myocardial excitable properties remain to be defined.

Human Studies

Since ancient times, the physician has been keenly attuned to the effects of psychologic factors on heart rhythm. But such relations have eluded scientific validation. The classic studies of Cannon[85] suggested that the biologically active amine "adrenaline" was secreted in response to stimuli that produced fear and rage reactions in animals, and he considered these biogenic amines to play a role in Voodoo death.[86] That emotions play a role in sudden death has gained currency by repetition if not by precise documentation. It is worth first considering the effect of higher neural activity on ventricular arrhythmia and then its possible role in sudden death.

Ventricular Arrhythmias and Neural Activity

It is well established that catecholamines can evoke ventricular arrhythmias. Less appreciated is that vagal stimulation may abolish ventricular ectopic activity. These opposite neural effects were decisively demonstrated more than 40 years ago in a disquieting human experiment.[87] Six elderly patients received intravenous injections of 0.1 mg of adrenalin and continuous electrocardiograms were recorded. "In each case ectopic ventricular beats from multiple foci appeared within a minute and quickly increased in number. The height of the reaction took place within the first 2 minutes and at this time practically all the beats were of ectopic origin." Fifteen minutes later, when each patient was free of arrhythmia, 20 mg of the cholinergic drug, acetyl beta methylcholin chloride was administered subcutaneously and the adrenalin injection was repeated. In 4 of the 6 patients not a single ectopic beat occurred. Relevant are the findings that parasympathetic maneuvers in the form of carotid sinus massage[88–90] or administration of vagotonic agents[91,92] decrease the frequency of ventricular premature beats and abolish ventricular tachycardia. It has recently been demonstrated that in some patients digitalis drugs reduce or completely eliminate ventricular extrasystoles. This suppressive effect has been ascribed to enhancement of vagal activity.[93]

Vagal and sympathetic tone change diurnally. The sleeping-waking cycle represents a marked diurnal variation in behavioral and neural activity. Heart rate changes during sleep are mediated with both sympathetic and parasympathetic nervous outflow and are abolished with complete denervation. A significant reduction of ventricular premature beats was observed during sleep in ambulatory patients; this occurred in 78 percent of 45 patients who exhibited ventricular premature beats during 24 hour monitoring while awake.[94] There was also a significant shift in grade of ventricular premature beats. Although the maximal grade was 2.7 during waking hours, it was lowered to 1.8 during sleep ($P < 0.001$). These changes occurred irrespective of the presence, type and extent of heart disease. The observed reduction in frequency and severity of ventricular arrhythmia was related to the lower level of sympathetic tone and the vagotonia attending sleep.

The role of psychologic stress in provoking ventricular arrhythmia has wide clinical currency.[95,96] This relation is frequently noted in patients continuously monitored in coronary care units (Fig. 7). Although stressful situations may be associated with emergence of ectopic

activity (Fig. 8), reassurance and relaxation such as achieved by means of meditation may result in abatement of arrhythmia (Fig. 9 and 10).

In controlled studies we have demonstrated that standardized psychologic stresses may evoke advanced grades of ventricular premature beats (Fig. 11). Taggart et al.[97,98] systematically explored cardiac responses to diverse stresses induced by car racing, driving in traffic, public speaking and to thermal, physical or emotional stresses. Multiple ventricular ectopic beats emerged in 5 of 24 patients with ischemic heart disease while driving their own car along a familiar route.[96] Thirteen of these patients also showed significant ischemic S-T segment and T wave alterations. Public speaking exposed more than 6 ventricular extrasystoles/min in 6 of 23 normal subjects, and prolific ectopic activity in 5 of 7 patients with coronary artery disease. A single oral dose of 40 mg of the beta adrenergic blocking drug oxprenolol suppressed these abnormalities.[98] Paroxysms of ventricular tachycardia have been related to profound emotion and deep seated psychopathologic disturbance.[99] When the latter was mitigated, the arrhythmias

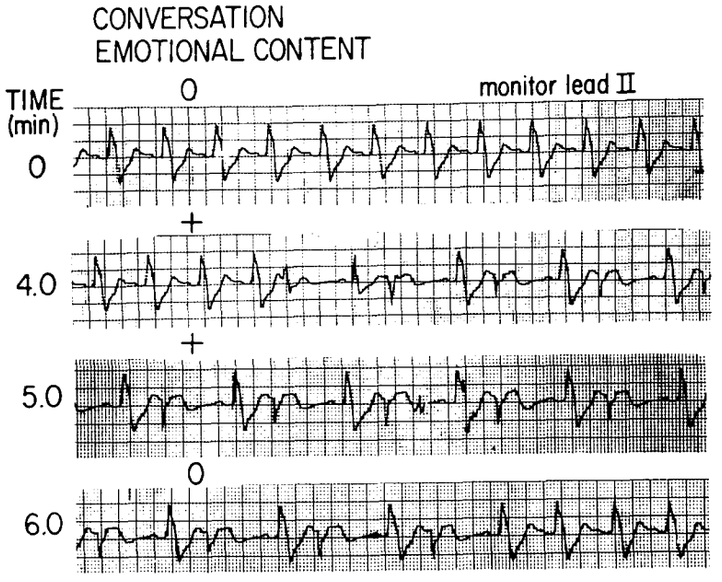

FIGURE 8. Lead II electrocardiogram a patient who had been free of ventricular ectopic activity during 48 hours of continuous monitoring. Within 4 minutes of initiating a conversation about family problems, ventricular bigeminy emerges and is sustained until the topic is shifted to a less emotionally charged content at 6 minutes.

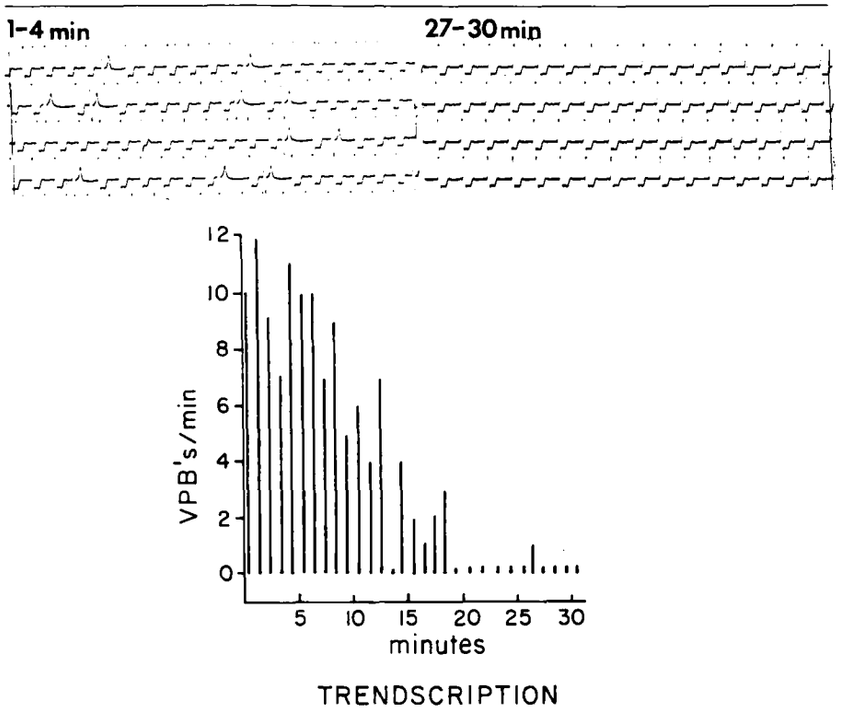

FIGURE 9. In a patient with rheumatic mitral insufficiency, the tension of anticipating medical advice to have valve replacement evokes frequent ventricular ectopic activity. During the 10th to 20th minutes, when reassurance is provided that surgery is not necessary, there is reduction and finally complete cessation of arrhythmia. VPB's = ventricular premature beats.

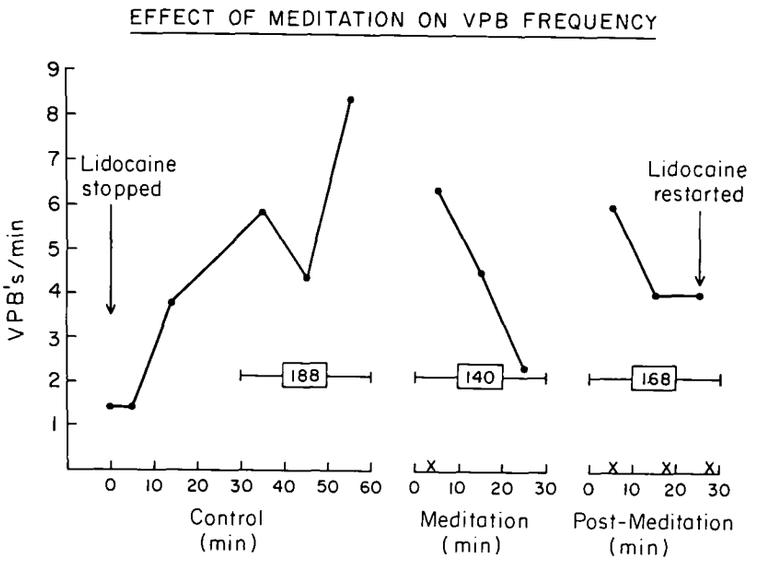

FIGURE 10. In a patient with high grade ventricular arrhythmia there is a marked increase in ventricular premature beat (VPB) frequency with omission of lidocaine. Premature beats are reduced by 20 minutes of meditation but increase in the postmeditation period.

were controlled.[100,101] Although evidence to date is preliminary, there can be little doubt that enhanced sympathetic activity may induce ventricular ectopic activity, and under some circumstances vagal discharge can diminish and may even entirely abolish ventricular premature beats. Because intense emotional states are associated with release of various biogenic amines that exert profound cardiovascular effects, an association between levels of psychologic activity and arrhythmias is to be expected.

Available evidence indicates that in man, as in the experimental animal, catecholamine administration can induce ventricular arrhythmia, whereas vagal activity exerts an opposite effect. Furthermore, diverse stresses and various psychologic states in certain subjects provoke ventricular ectopic activity.

Sudden Death and Psychologic Factors

The possibility of a relation between psychologic factors and sudden death is subject to a surfeit of speculation and is buttressed by persuasive anecdotes whose lineage extends to the dawn of recorded history. Does the presumed association between intense emotions such as rage, fear, grief, humiliation, hopelessness and joy and sudden death represent folk lore or folk wisdom? Engel[102] speculates on the persistence of the idea of such an association and questions whether it represents mass delusion, to which man is all too prone, or whether it is possibly the expression of empirical folk wisdom that has provided medicine with fox glove for dropsy and lime juice for scurvy.

It is worth considering first the more elementary question of whether neural factors can be associated with the occurrence of sudden death. Perhaps the most suggestive biologic model is that presented by the various clinical entities subsumed under the rubric of prolonged Q-T interval syndromes. Schwartz et al.[103] have suggested that the sympathetic nervous system is implicated and have adduced the following reasons in support: (1) Syncopal attacks, which represent nonsustained episodes of ventricular fibrillation, are triggered by exertion and intense emotion; (2) the T

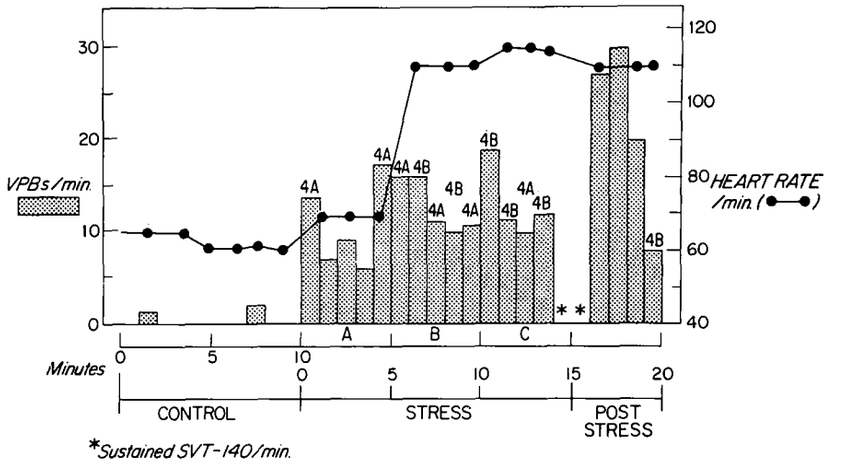

FIGURE 11. In a patient with recurrent ventricular fibrillation ventricular ectopic activity is largely abolished with antiarrhythmic drugs. High grade arrhythmia (4A = couplets, 4B = ventricular tachycardia) recurs during 15 minutes of psychologic stress testing and there is an associated sinus tachycardia. Stress is discontinued at the onset of supraventricular tachycardia (SVT), which persists for 2 minutes. VPBs = ventricular premature beats.

wave alterations that precede syncopal episodes can be reproduced by asymmetric sympathetic stimulation; and (3) beta adrenergic blocking drugs and ablation of the left stellate ganglion[104] may normalize the Q-T interval and prevent recurrent attacks.

Certain chronic emotional tension states have been associated with an increased prevalence of sudden death. Bereavement has been shown to increase susceptibility to such sudden fatality.[105] During the first 6 months after loss of a spouse, 4,486 widowers, 55 years of age or older, had an increment in death rate that was 40 percent above the expected rate for married men matched for age. Rahe et al.[106,107] retrospectively interviewed the families of 226 victims of sudden coronary death in Helsinki, Finland and noted significant life changes such as divorce, grief and altered work patterns in the 6 months preceding death compared with status during the same time interval 1 year earlier. Chronic depression further increased by anxiety, anger and changes at work were reported by 26 widows to have preceded the sudden death of their husbands.[108] Among patients recovering from acute myocardial infarction, ward rounds proved to be a risk factor.[109] A fivefold greater incidence of sudden death occurred during medical daily ward rounds than would have been anticipated had these deaths been random. The physician-in-chief's round, held only once weekly, accounted for half the sudden deaths.

Direct evidence demonstrating a cause and effect relation between psychologic factors and sudden death will be difficult to establish with certainty. However, in an individual patient such a causal relation may on occasion appear probable. This is illustrated in one recent report.[110] The patient, a 39 year old man, twice experienced ventricular fibrillation and had frequent ventricular premature beats. He had normal coronary arteries and no indications of structural heart disease. Evidence adduced for higher nervous activity in the genesis of the ventricular arrhythmia included the psychiatric makeup of the patient, the emotional stress attending the first cardiac arrest, the provocation of advanced grades of ventricular premature beats and ventricular tachycardia by psychiatric visits, the prevalence of arrhythmia during the rapid eye movement (REM) stage of sleep when he had violent dreams, the occurrence of the second episode of ventricular fibrillation during a similar period of sleep and the fact that meditation and a cardioselective beta adrenergic blocking drug decreased ventricular ectopic activity.

If emotional 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 sudden death. Three recent studies provide support for this view. In patients who had recovered from acute myocardial infarction, the incidence of sudden death was significantly reduced with the use of beta adrenergic blocking drugs.[111–113]

Final Comments

The evidence reviewed indicates that higher nervous system activity can trigger ventricular arrhythmias including ventricular fibrillation and that the sympathetic limb of the autonomic nervous system plays a key role. For too long the heart and vasculature have been deemed a self-contained system. Arrhythmias have been related to anatomic derangements within the myocardium and have been treated by altering one or another property of cardiac excitability. Resolution of the problem of sudden death requires that the central nervous system be restored to its premier integrating role in cardiac function. Whereas in most spheres of science mechanistic models have largely been discarded, an isolated system approach still prevails in medicine. The profound recent advances in neurochemistry and psychopharmacology promise new insights into cardiology and present a challenge and opportunity for reintegrating heart and mind. Such integration not only will enrich clinical understanding but also should diminish the gulf between the art and the science of contemporary medicine.

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