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Role of Emotions and Stress in the Genesis of Sudden Death

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Emotional arousal induces dramatic endocrine responses through either the sympathetic-adrenal medullary system or pituitary-adrenal cortical system. Many of the known actions of cortisol and catecholamines are atherogenic, cardiotoxic and arrhythmogenic. Emotional stress can produce sudden cardiac death in experimental animals, as can the administration of exogenous catecholamines. Previous studies have found that emotional stress is a common precursor to sudden cardiac death. Thus, acute neuroendocrine arousal, superimposed on a substrate of compromised myocardium and electrical instability, may constitute an important, final inciting event in sudden cardiac death.

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History is replete with anecdotes of persons who died suddenly in the throes of intense emotion. Now scientific study is beginning to shed light on the pathways and mechanisms responsible for these observations.

Neuroendocrinology of Stress and Emotion

Two pathways of physiologic responses to stress. Previous work (1,2) has demonstrated that emotion is capable of both eliciting powerful physiologic responses and recruiting distinct and selective pathways. However, such responses are always based on perceptual coloring of the environmental event. The two distinct pathways, pituitary-adrenal cortical activation or sympathetic-adrenal medullary activation, occur during confrontations between various members of a social group as they seek food, territory, mates and so forth. Social interactions eliciting competitive behavior in an attempt to maintain status and prevent threatened loss of esteem or related objects of attachment result in the alarm reaction associated with activation of the sympathetic-adrenal medullary system. Conversely, social interactions leading to vigilance and downward displacement in the hierarchy are associated with stimulation of the pituitary-adrenal cortical system accompanied by excess cortisol, mental depression, decreased gonadotropin levels, enhanced vagal activity, gluconeogenesis and pepsin production. Experimental animal studies (3) provide numerous examples of induced emotional stress creating various forms of cardiovascular disease including hypertension, myocardial fibrosis, myocardial infarction and sudden cardiac death.

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Among the known physiologic effects of sympathetic-adrenal medullary activity represented by catecholamines are those of enhanced lipid mobilization, increased platelet adhesiveness and aggregation, lowered threshold to arrhythmia generation, increased secretion of glucagon, thyroxine, calcitonin, parathyroid hormone, renin, erythropoietin and gastrin, diminished insulin secretion and diminished myocardial efficiency through wasting oxygen in a disproportionate fashion. The intense adrenergic activity associated with pheochromocytoma can result in a hypertensive crisis, myocardial infarction with or without coronary disease, malignant rhythm disturbances and catecholamine-induced myocarditis.

Effects of excessive glucocorticoid production. The alternate pathway of vigilance results in excessive production of glucocorticoids (4). Glucocorticoids convert proteins into carbohydrate and fat, have a minor antagonistic effect on insulin, promote the development of diabetes, foster hyperlipidemia and hypercholesterolemia, enhance water diuresis, diminish circulating lymphocytes, reduce leukocytosis and polycythemia, increase platelet mass, lower the electrical excitation threshold of the brain, increase gastric acidity and pepsin production, block growth hormone secretion, decrease calcium absorption, enhance angiotensinogen production, sensitize arterioles to the pressor effect of catecholamines, decrease the inflammatory reponse and increase sodium retention through mineralocorticoid effects.

Regarding cardiovascular effects of glucocorticoids, it is generally accepted that they increase serum lipids, increase atherosclerosis in dogs fed an atherogenic diet and increase the number of dead or injured cells in the arterial endothelium. The administration of corticosteroids has been associated with acceleration of atherosclerosis in patients with rheumatoid arthritis (5). In addition, morning cortisol levels

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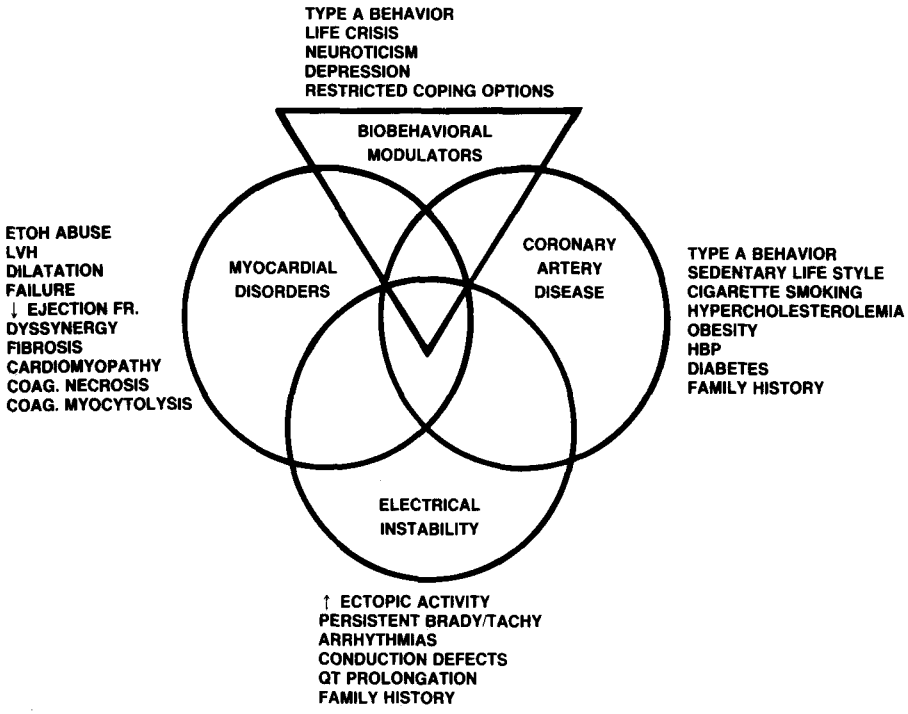


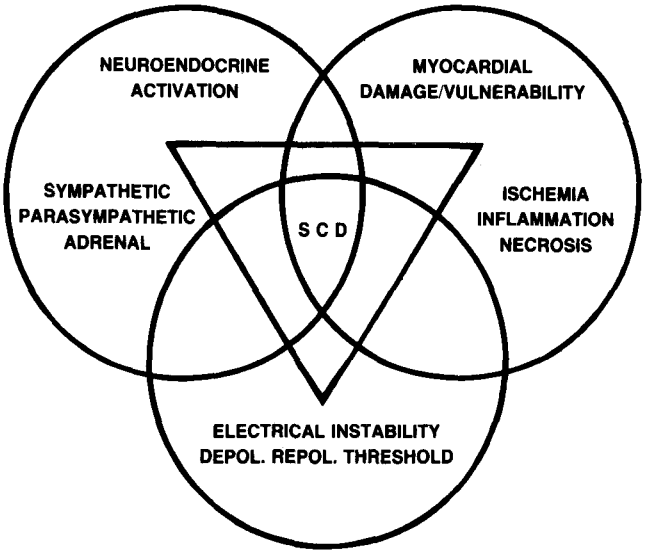
Figure 1. Risk factors for sudden cardiac death. Brady/tachy = Bradycardia/tachycardia; COAG. = coagulation; HBP = high blood pressure; FR. = fraction; LVH = left ventricular hypertrophy; ↓ = decreased; ↑ = increased.

have been found to be higher in patients with severe coronary atherosclerosis than in patients with minimal or no disease (6). Naturally occurring excesses such as those associated with Cushing's syndrome frequently result in accelerated atherosclerosis, hypertension and suicide.

Emotional Stress and Sudden Death

Excessive sympathetic activity. Anecdotes from folklore are supported by several epidemiologic and pathophysiologic observations that appear to strongly link emotional stress to sudden death (7). A key point is that time frames importantly influence what is seen in postmortem examinations. In the experience of Cobb et al. (8), the majority of victims of sudden cardiac death who are resuscitated do not have electrocardiographic evidence of acute myocardial infarction. Furthermore, coagulation necrosis does not appear to be a predominant histologic contributor to acute or sudden cardiac death. In the study of Baroldi et al. (9), of 208 witnessed sudden cardiac deaths, only 75% of the victims had significant coronary obstructive disease and less than 20% had either an acute occlusive thrombus or coagulation necrosis. These findings are consistent with the clinical reports of Cobb et al. (8). However, nearly half of the cases showed excess heart weight, four-fifths showed myocardial fibrosis suggesting an old inflammatory or damaging process and more than 85% of the cases were associated with coagulative myocytolysis, a type of hyperfunctional necrosis. These lesions are also seen in those dying of head injuries and pheochromocytoma and may be easily produced in animal models by administration of exogenous catecholamines (10). The lesions appear in a matter of seconds to minutes and disappear within approximately 24 hours. The following residua leave only a pattern of empty sarcolemmal tubules that are subsequently replaced by patchy myocardial fibrosis. Thus, it appears that repeated excesses of sympathetic activity are capable of creating myocardial damage. Furthermore, the characteristic lesions of cate-

Figure 2. Pathophysiologic pathways in sudden cardiac death (SCD). DEPOL. = depolarization; REPOL. = repolarization.



cholamine excess are seen in more than 85% of sudden cardiac deaths.

Contributory factors in sudden cardiac death. Thus, an overview of sudden cardiac death appears to involve several destructive factors (Fig. 1). Certainly one of the most prevalent is that of coronary artery disease accelerated by a variety of risk factors, many of which are linked to or aggravated by emotional stress (11). The second major factor is that of electrical instability that ultimately may culminate in a malignant rhythm disturbance. The third major pathologic component is that of a myocardial disorder. It is through this pathway that coronary artery disease most likely exerts its influence by rendering the myocardium vulnerable, jeopardized or blighted. The fourth contributing factor represents the essential point of this discussion, namely, that of biobehavioral modulators or emotional stress.

Psychological factors, coronary disease and risk of sudden death. The epidemiologic reports (12) linking stress to coronary heart disease are too extensive to be discussed in any comprehensive fashion; however, where studied specifically, acute psychological stress is strongly associated with sudden cardiac death (13). Recent life changes and a history of psychiatric illness have also been strongly correlated with the risk of sudden cardiac death (14). Recent loss of a loved one also enhances the risk of sudden cardiac death (15). When viewing the numerous reports on psychosocial variables and risk for coronary heart disease, the general rule is that those variables most closely expected to involve intense sustained overstimulation of the central nervous system have the most consistently positive associations with risk. Thus, there is considerable evidence suggesting that coronary disease and risk of sudden death are strongly associated with anxiety, depression, sleep disturbances, fatigue and emotional drain. More distant variables such as social mobility, migration and educational level are less uniformly likely to cause intense central nervous system arousal and are therefore less predictably and strongly associated with risk.

Emotional stress and cardiac arrhythmias. Although neuroendocrine arousal is capable of causing direct myocardial damage that may enhance electrical instability, it is also true that emotional stress can elicit disordered cardiac rhythms directly (16). Lethal arrhythmias can be provoked experimentally in animals by electrical stimulation of the brain and occur spontaneously in patients with subarachnoid or intracerebral hemorrhage. The ability of increased sympathoadrenal medullary activity to lower the threshold to ventricular fibrillation has been demonstrated in a multitude of studies. Conversely, beta-receptor blockade or parasympathetic enhancement, or both, appears to confer protection to arrhythmogenesis. In addition, maneuvers that decrease central sympathetic tone by increasing brain serotonin levels have conferred effective protection from arrhythmias in both ischemic and normal hearts under psychological stress.

Three spheres of activity and sudden cardiac death. Thus, it is apparent that sudden cardiac death is the result of three interrelated spheres of activity (Fig. 2). Myocardial damage and vulnerability may be effected through ischemia, inflammation or necrosis, and this "softening up" process has usually occurred on a long-term basis before the final event. The second sphere of activity is that of electrical instability and diminished threshold to the ventricular ectopic activity that culminates in sudden death. The third interlocking sphere of activity is that of neuroendocrine activation. Neuroendocrine arousal is capable of creating myocardial damage as well as independently inducing malignant rhythm disturbances. Studies by Reich et al. (17) suggest that approximately 20% of resuscitated victims of sudden death have no structural heart disease. In these cases, lethal arrhythmias may be precipitated exclusively by psychological stress.

Implications. Intense emotional arousal mediated through the limbic system is capable of provoking neuroendocrine excesses of both sympathetic-adrenal medullary and pituitary-adrenal corticol systems. The cardiotoxic properties of excessive amounts of these hormones have been discussed in terms of their potential to create the correct milieu for the development and expression of 20th century cardiovascular disease. These expressions include hypertension, atherosclerosis, cardiomyopathy, arrhythmogenesis and sudden cardiac death. The likelihood that these pathways are injurious is strengthened by a variety of epidemiologic and experimental observations strongly linking emotional stress to sudden cardiac death.

It would appear that future clinical investigations should monitor physiologic reponses to psychological challenge in a controlled stressful environment (18) to determine those individuals who recruit excessive neuroendocrine responses and show evidence of cardiovascular deterioration under such stressful conditions. Our preliminary experience suggests that life stress simulation testing is a clinically useful and discriminating technique for determining who may be at risk for future coronary events (19). The goals of further understanding the role of emotion and stress in the genesis of sudden death and of identifying its potential victims before the fact remain both a challenge and an avenue to better medical care for those at risk of sudden cardiac death.

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