Psychosocial factors in sudden cardiac arrest

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INTRODUCTION

Awareness of the ability of severe emotional stress to provoke sudden death has been present throughout recorded history. However, the relationship of psychosocial factors to cardiovascular disease, and in particular sudden cardiac death, has been difficult to quantify. This has been due to several reasons:

- It is difficult to objectively quantify emotional stress.
- Research has until recently been more focused on the chronic factors leading to the development of coronary artery disease rather than on the precipitation of acute coronary syndromes once such disease is present.
- The division between the social science and medical science investigators have impeded dialogue.
- There are inherent difficulties in accurately assessing the triggers of sudden death.

Despite these limitations, the weight of evidence for a role for psychosocial factors in sudden cardiac death has become compelling and in one review of 96 published studies on this topic, a positive association was observed in 92 percent [1]. New studies are therefore warranted to determine whether behavioral and pharmacologic interventions will lower cardiovascular risk [2].

Since acute myocardial infarction is an important precipitant of ventricular fibrillation and sudden death, many of the advances in understanding the pathophysiology of acute myocardial infarction are applicable for sudden death (see "Psychosocial factors in acute coronary syndrome"). In addition, emotional stress may lower the threshold for arrhythmia both directly and secondary to the provocation of transient myocardial ischemia.

CIRCADIAN VARIATION

The task of accurately determining the time of occurrence of sudden cardiac death is often difficult for two main reasons: a possible inability to ascertain if a sudden cardiac event is actually the cause of death; and the occurrence of unwitnessed deaths, often at night, for which time of death is uncertain. Despite these limitations, a circadian variation has been found for sudden cardiac death that parallels that of myocardial infarction, with a peak in the morning. It has been suggested that a primary arrhythmic event is more likely to occur in the morning because increased adrenergic activity at this time may increase electrical instability or induce myocardial ischemia without infarction.

Evidence in support of this relationship was initially obtained from data from two large databases and from a number of other studies with a lower specificity of diagnosis. Mortality reports of the Massachusetts Department of Public Health were utilized to determine the time of sudden death [3]. Analysis was performed in the group of 2203 individuals who in 1983 died an out-of-hospital death from ischemic heart disease one hour or less after the onset of symptoms. The peak frequency of sudden death was between 9 and 11 AM (figure 1).

A report from the Framingham Heart Study evaluated coding forms of 264 "definite" sudden cardiac deaths (11 percent of total deaths) and 165 "possible" sudden cardiac deaths (7 percent of total deaths) [4]. The exact time of death was known in most cases but, for some, it was necessary to estimate the interval in which the death occurred. In such instances, the probability of death was evenly distributed over the estimated interval.

The time of occurrence of definite sudden cardiac death exhibited a prominent circadian variation with a low frequency during the night, as would be expected from the requirement that the death be witnessed. However, a circadian variation remained when patients with possible sudden cardiac death (particularly those with unwitnessed deaths between midnight and 6 AM) were added to those with definite and witnessed sudden cardiac death. The hourly risk of sudden cardiac death was at least 70 percent greater between 7 and 9 AM than the average risk during the remaining 22 hours of the day.

Similar observations were made in later studies [5-8]. As an example, data from the Berlin emergency care system found a peak frequency of ventricular fibrillation between 6 AM and noon; in contrast, asystolic episodes were more evenly distributed throughout the day [6]. The morning peak in sudden death is particularly related to the first three hours after awakening and onset of activity [7]; a similar relationship has been noted with myocardial ischemia (see below).

Data from the Seattle Fire Department, based upon 6603 cases of out-of-hospital cardiac arrest, of which 3690 were witnessed, also exhibited a diurnal variation, with a low incidence at night and two peaks of approximately the same size [9]. An evening peak at 4 to 7 PM was attributed primary to patients found in ventricular fibrillation, while arrests that showed other rhythms exhibited mainly a morning peak from 8 to 11 AM. There were 597 patients who had at least two separate cardiac arrests, but there was no association between the times of the first and second arrests, suggesting that the diurnal patterns for cardiac arrest are associated with patterns of daily activity rather than characteristic of the underlying cardiac disease (figure 2).

Seasonal variation — In addition to the diurnal variation, cardiac arrests also show a weekly and seasonal variation; the daily incidence peaks on Monday and the seasonal incidence is greatest in the winter [8,10]. As an example, one 12-year analysis of 222,265 cases of death from coronary heart disease found that there were approximately 33 percent more deaths in December and January than in June through September; this was only partly explained by temperature variability [11].

Holter monitoring and ICD — The above studies are somewhat limited by their frequent reliance on eyewitnesses to determine the timing of sudden cardiac death. More objective data has come from Holter monitoring and the implantable cardioverter-defibrillator (ICD). In a study of 164 ambulatory patients evaluated with 24-hour Holter monitoring, for example, a morning peak of ventricular premature beats was consistently present for each of three consecutive days of observation [12]. In another series, the peak incidence of sustained symptomatic ventricular tachycardic episodes in 68 patients occurred between 10 AM and noon [13].

The ICD provides a better opportunity to firmly establish the timing of malignant tachyarrhythmias, which are the most common cause of sudden cardiac death [14-16]. As an example, a prominent circadian pattern of ventricular arrhythmias was demonstrated in a series of 483 patients who had an ICD implanted between 1990 and 1993 [14]:

- For rapid tachyarrhythmias (>250 beats/min), a three-hour peak was present between 9 AM and noon (22 percent of total episodes) and a three-hour minimum occurred between

3 and 6 AM (4 percent of episodes, p <0.001).

- A similar circadian pattern characterized by a 9 AM to noon peak was also observed for less rapid tachyarrhythmias.

- The circadian pattern is similar for those with ischemic or nonischemic heart disease [16].

Depression appears to increase the rate of appropriate shocks in patients with an ICD. This was illustrated in a report from the Triggers of Ventricular Arrhythmia Study (TOVA) in which 645 patients were followed, 4 percent of whom had moderate to severe depression [17]. Moderate to severe depression was significantly associated with the time to first shock and with all shocks for VT/VF (hazard ratio 3.2 overall and 6.4 in the 476 patients with coronary heart disease).

Myocardial ischemia — In some cases, sudden cardiac death may be provoked by transient myocardial ischemia in the absence of infarction. Several series have found that the frequency of both symptomatic and asymptomatic ST-segment depression is maximal in the morning [18,19].

The hypothesis that the morning increase in myocardial ischemia is related to time of awakening rather than to the time of day was evaluated in 32 patients with angina in whom the time of awakening was known [20]. The peak activity was found to occur in the first two hours after rising.

Another study investigated the relationship between the patient's perceived level of mental activity and ST depression during daily life [21]. Most ischemic episodes occurred during activities classified as "usual" physical or "usual" mental activity; and only a minority occurred during situations that the patient described as stressful. However, when the duration of ST depression was divided by the total time spent in each category, transient ischemia was more likely to occur as the intensity level of mental activity increased. Mental activities appear to be as potent as physical activities in triggering ischemia.

Beta blockers affect this circadian pattern, blunting the morning increase in sudden death and ventricular tachyarrhythmias [22,23]. However, other antiarrhythmic drugs do not have the same effect. In the CAST study, for example, a prominent morning peak was present in patients receiving encainide, flecainide, and moricizine [24]. Amiodarone also appears to have no effect on the circadian pattern of sudden cardiac death [25].

EMOTIONAL STRESS AND ARRHYTHMIA

Despite the numerous anecdotes relating emotional stress to the precipitation of arrhythmia, there has not been much systematic study of this relationship. One report evaluated the psychologic precipitants in 117 patients with life-threatening arrhythmias [26]. In 25 subjects (21 percent), a presumed psychologic trigger was found, the most common of which was anger. The lack of a control group in this study prevented estimation of the relative risk of anger. However, in a series of patients with nonfatal myocardial infarction in which control data were available, episodes of anger were associated with a doubling of risk which was present for two hours prior to onset of symptoms [27].

The role of stress on the occurrence of arrhythmia is likely mediated by sympathetic activation and an increase in circulating catecholamines, which can alter the induction, rate, and termination of ventricular arrhythmia. This was evaluated in 18 patients with a history of ventricular tachycardia and an ICD who underwent noninvasive electrophysiologic test in baseline and during mental stress [28]. During mental stress the ventricular tachycardia was faster and more difficult to terminate, and correlated with an increase in norepinephrine levels >50 percent above baseline.

Intense stressors, such as earthquakes, have been associated with increased cardiac mortality [29]. In one study of patients with ICDs, the destruction of the World Trade Center in New York City on September 11, 2001 was associated with a significant increase in episodes of tachyarrhythmia, both among patients living in the New York City area and remotely [30,31]. Similar effects have been noted for the frequency of acute myocardial infarction. (See "Psychosocial factors in acute coronary syndrome".)

A diagnosis of cancer may increase the risk of cardiovascular death. A cohort study using multiple registries examined the risk in more than 6,000,000 Swedes from 1991 through 2006; compared with cancer-free individuals, patients diagnosed with cancer were six times more likely to die from cardiovascular causes within one week of receiving the diagnosis (relative risk 5.6, 95% CI 5.2-5.9) [32].

Several large-scale, community based studies have found a significant dose-dependent relationship between anxiety disorders and cardiac death [33]; the excess risk was confined to sudden death and the relative risk for men with high phobic levels was 6.08 after adjusting for other cardiovascular risk factors [34,35].

Although certain behavior patterns, such as type A behavior, have been implicated in sudden death, these relationships have not been widely accepted as causal. There are several reasons for this lack of acceptance including certain components, such as hostility, appearing more predictive, and the difficulty in standardizing measures for these behavior patterns and in

extrapolating the results of laboratory studies of reactivity to the "real world." In addition, changes leading to sudden death may be transient, thereby limiting their ability to be well evaluated in the chronic state.

Despite these limitations, a large body of data convincingly demonstrates that depression and hostility are behaviors that are associated with an increased risk of coronary heart disease related events [33,36-38]. As an example, a prospective study using an interview measure of depression found that the 16 percent of patients with major depression had a five-fold higher mortality that was independent of their underlying cardiac status; sudden death as the mode of death was particularly increased in these patients [38].

Other psychosocial factors, such as low education attainment (less than high school graduation), social isolation, and absence of emotional support have also been associated with increased mortality following myocardial infarction [36,39-41]. In addition, bereavement, divorce, and job loss have been associated with an increased risk of sudden death, which may be related to a combination of both arousal and depressive states [42,43].

One area of potential intersection between emotional stress and sudden death that has received relatively little attention has been dreaming and REM sleep. Anger or fear are expressed in over one-half of all dreams [44,45], and there may be marked surges in sympathetic activity during REM sleep [46]. While sleep is overall a protected time with regard to cardiovascular events, violent or frightening dreams have been associated with ventricular fibrillation [47]. The increased morning frequency of cardiovascular events described above could in part be due to bursts of REM sleep prior to awakening.

Pathophysiology — Controlled animal experiments provide considerable support for anger as a trigger of arrhythmia, particularly in the presence of coronary narrowing. As examples:

- Stimulation of the hypothalamus, which plays a major role in the regulation of the autonomic nervous system, can induce ventricular tachyarrhythmias [48,49]. This response is inhibited by beta blockade, suggesting that increased sympathetic activity is the likely cause [50].

- Provocation of anger in dogs resulted in a 30 to 40 percent reduction in the threshold for inducing repetitive extrasystoles, which is a surrogate measure of the ventricular fibrillation threshold [51]. This enhanced vulnerability, which was associated with an increased magnitude of T-wave alternans, was also markedly reduced by beta blockade.

A figure provides a schema for considering the mechanism by which acute emotional stressors such as anger may trigger ventricular arrhythmia (figure 3). While a tachyarrhythmia is the

major response to an emotional stressor, a vagal response leading to bradycardia and hypotension may lead to syncope. This vasovagal condition is usually benign, unless occurring in the presence of significant conduction system disease [52].

An increase in sympathetic activity and a decrease in vagal tone are principal components of the response to anger. The result is a significant elevation in heart rate and blood pressure which could lead to increased myocardial oxygen demand and transient ischemia. The magnitude of the heart rate response and the double-product (heart rate x blood pressure) are typically less during mental tasks than during exercise stress. This suggests that a primary reduction in myocardial oxygen supply might be present during mental stress-induced ischemia. Constriction of atherosclerotic coronary artery segments has been demonstrated in dogs two to three minutes following elicitation of anger [53]. The coronary vasoconstriction persisted after the return of heart rate and blood pressure to baseline and could be blocked by the alpha-receptor antagonist prazosin.

Sympathetic nervous system stimulation increases cardiac vulnerability in the normal and ischemic heart [54,55]. This response is manifested by the spontaneous occurrence of arrhythmia, reduction in the ventricular fibrillation threshold, and increase in the magnitude of T-wave alternans [56,57]. A second peak of vulnerability has been described after reperfusion of an occluded coronary vessel, possibly due to the washout of ischemic byproducts [58].

Increased sympathetic activity enhances cardiac vulnerability in several ways:

- An imbalance of oxygen supply-demand due to increased cardiac metabolic activity and coronary vasoconstriction, particularly in vessels with injured endothelium.
- Direct profibrillatory influences may result from changes in impulse formation, conduction, or both [59].
- Potentiation of Purkinje fiber automaticity, early depolarizations, and prolongation of the QT interval may lead to a reduced threshold for ventricular fibrillation.
- Catecholamine-induced hypokalemia, resulting from the intracellular movement of potassium in response to beta-2-adrenergic stimulation, may potentiate arrhythmia, and may provide insight into the protective effect of beta blockade [60].

Lowering of vagal activity with stress may also contribute via the following effects: reduced presynaptic inhibition of norepinephrine release; increase in heart rate with its attendant cardiac metabolic demands, and lowering of the threshold for ventricular fibrillation [61]. In humans, reduced vagal tone, as assessed by heart rate variability, is associated with increases in

mortality and the incidence of sudden death among postinfarction patients [62]. (See "Incidence of and risk stratification for sudden cardiac death after myocardial infarction".)

Acute psychologic stress may also lead to plaque rupture and thrombosis, possibly triggering the onset of ventricular fibrillation [63]. (See "Mechanisms of acute coronary syndromes related to atherosclerosis".) A prothrombotic contribution was supported by the finding of increases in fibrinogen, von Willebrand factor and D-dimer in individuals subject to the Hanshin-Awaji earthquake [64].

PREVENTIVE MEASURES

In summary, considerable data supports a role for psychosocial factors in sudden death — both acutely with anger and chronically with states of depression, hostility, and social isolation. Although successful interventions remain less well established, an important mechanism of the cardioprotective effect of beta blockers after myocardial infarction may be through modification of acute stressors. Beta blockade is more protective against sudden death than non-sudden death, reducing non-sudden death by 20 percent, sudden death postinfarction by 33 percent, and witnessed instantaneous death by 46 percent [65,66]. However, a recent study of patients with an ICD found that standard doses of beta blockers did not appear to alter the circadian pattern in the onset of sustained ventricular tachycardia [67].

The mode of action of beta blockers is not completely understood, but includes:

- Direct sympathetic blockade
- A membrane stabilizing effect
- A reduction in ischemic potential
- An increase in heart rate variability and baroreflex sensitivity [68-70]
- A shorter corrected QT interval
- Prevention of stress-induced hypokalemia [60]

Other pharmacologic therapies show some promise. In the ONSET study, aspirin was noted to reduce the relative risk of nonfatal myocardial infarction following anger [27]. Parasympathomimetic stimulation with low dose scopolamine show some promise in increasing vagal activity and heart rate variability, and trials evaluating antidepressant therapy with serotonin uptake inhibitors may be appropriate in selected individuals.

Implementation of low-cost psychosocial interventions warrants serious consideration postmyocardial infarction, although current evidence is insufficient to justify widespread implementation. An initial report suggested benefit from such an approach; however, this was

not confirmed in a later trial [71]. It is hoped that more definitive information will be provided by a multicenter psychologic intervention trial begun by the National Institutes of Health to test practical strategies in patients following myocardial infarction.

There are patients in whom an avoidable potential trigger occurs with such regularity that the accumulated risk becomes substantial and intervention may be helpful. As an example, a patient who experiences anger, a known trigger, many times per day might benefit from stress management instruction. In addition, patients taking anti-ischemic or antiarrhythmic medication should have adequate pharmacologic coverage during the full 24-hour period, particularly during the morning period of increased risk.

From a research perspective, further attempts to identify the mechanism by which psychosocial factors increase risk of sudden death are needed, as well as the testing of interventions to lower the risk. Interventional trials are currently limited. Such strategies may work indirectly by promoting healthy behavior such as smoking cessation, diet control, and compliance with other medical recommendations or directly by modifying physiologic factors such as sympathetic nervous system activity, coronary blood flow and resistance, platelet aggregation and thrombotic potential, plaque stability, and lipid metabolism.

SUMMARY AND RECOMMENDATIONS

- Evidence suggests a possible role for psychosocial factors in sudden cardiac death. (See 'Introduction' above.)
- A circadian variation has been found for sudden cardiac death that parallels that of myocardial infarction, with a peak in the morning. It has been suggested that a primary arrhythmic event is more likely to occur in the morning because increased adrenergic activity at this time may increase electrical instability or induce myocardial ischemia without infarction. (See 'Circadian variation' above.)
- Cardiac arrests also show a weekly and seasonal variation. The daily incidence peaks on Monday and the seasonal incidence is greatest in winter. (See 'Seasonal variation' above.)
- Data from an implantable cardioverter-defibrillator (ICD) study found that depression appears to increase the rate of appropriate shocks in patients with an ICD. (See 'Holter monitoring and ICD' above.)
- There have been few studies of the relationship between emotional stress and precipitation of arrhythmia. The hypothesized role of stress in the occurrence of

arrhythmia is likely mediated by sympathetic activation and an increase in circulating catecholamines, which can alter the induction, rate, and termination of ventricular arrhythmia. (See 'Emotional stress and arrhythmia' above.)

- There are no well-established interventions for ameliorating the possible role of psychosocial factors (such as anger, depression, and social isolation) in sudden death. The cardioprotective effect of beta blockers after myocardial infarction may work through modification of acute stressors. (See 'Preventive measures' above.)

- There are patients in whom an avoidable potential trigger occurs regularly that an intervention may be helpful. As an example, a patient who experiences anger many times per day might benefit from stress management instruction. (See 'Preventive measures' above.)

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