Sudden Cardiac Death
Support for a Role of Triggering in Causation

Stefan N. Willich, MD, MPH; Malcolm Maclure, ScD; Murray Mittleman, MD, MPH; Hans-Richard Arntz, MD; and James E. Muller, MD

Recent advances suggest an important role of triggering in causation of sudden cardiac death, a disorder that remains one of the most complex and difficult problems of contemporary medicine, afflicting at least 300,000 individuals each year in the United States alone.1-4 Understanding of triggering may provide a basis for improved prevention, the most promising strategy for reducing the mortality caused by the disease.

The need for renewed focus on identification of the mechanisms causing sudden cardiac death is strengthened by the unexpected results of the Cardiac Arrhythmia Suppression Trial (CAST). The CAST finding that suppression of nonsustained ventricular ectopy by class 1C antiarrhythmic agents is associated with increased mortality calls into question the causal role of ventricular premature beats in the onset of sudden cardiac death.5

The role of external events and the nature of the pathophysiological mechanisms causing sudden cardiac death are poorly understood, partly because of the obstacles inherent in studies of the disorder. The observation of a circadian variation in the incidence of sudden cardiac death with a significant morning peak provides the opportunity to identify processes that might be causal.6,7 This approach is strengthened by the findings of similar circadian patterns for nonfatal myocardial infarction,8,9 transient myocardial ischemia,10,11 and ventricular12-14 and supraventricular15 arrhythmias. The morning increase in the occurrence of these related disorders suggests causation by identifiable triggers.16

In addition to these epidemiological observations, an opportunity for a better understanding of the disorder is provided by recent pathological findings in the coronary arteries of patients with sudden cardiac death17-20; recognition of the significance of increased platelet aggregability,20-23 decreased fibrinolytic activity,24,25 and other blood components involved in thrombogenesis26; and identification of morphological and functional abnormalities of myocardial tissue that increase its arrhythmogenic potential.27-30

Various Definitions of Sudden Cardiac Death
The heterogeneity of definitions of sudden cardiac death creates difficulty in interpreting and comparing studies of the disorder and in formulating hypotheses of pathophysiological mechanisms. The time interval from onset of symptoms to death has been defined by some investigators and organizations as less than minutes but by others as up to 24 hours.31-33 Furthermore, some definitions include sudden cardiac deaths occurring in the presence of cardiac disorders that are associated with increased risk of sudden cardiac death, including cardiomyopathy, valvular heart disease, and congenital abnormalities, whereas others exclude patients with evidence of prior heart disease. For the purposes of the present article, we will define sudden cardiac death as cardiac death (in the absence of an apparent noncardiac cause of death) that occurs within 1 hour after onset of symptoms in patients without valvular heart disease or congenital cardiac abnormalities. This definition includes deaths caused by a primary arrhythmia and those caused by an arrhythmia preceded by ischemia.

Epidemiological Findings
Documentation of Circadian Variation in the Onset of Sudden Cardiac Death

Determination of the distribution of times of sudden cardiac death in a population is difficult because of 1) the problem of ascertaining whether or not a sudden cardiac event was actually the cause of death, 2) the occurrence of unwitnessed deaths for which the time of death as well as cause of death is uncertain, 3) the increased likelihood that such unwitnessed deaths would occur at night, and 4) the large number of subjects needed to detect a circadian pattern.

Before the recent surge of interest in timing of onset of cardiovascular diseases, several studies suggested a lower incidence of sudden cardiac death during sleep than at other times.32-35 Only 12% of cases of sudden cardiac death occurred during sleep, less than half of the 33% expected during 8 hours of sleep if the events were uniformly distributed throughout the 24-hour period.

The first direct evidence of a circadian variation of sudden cardiac death was reported in 1987 from a retrospective analysis of the mortality records of the Massachusetts population.6 Since sudden cardiac death is not uniformly coded in the International Classification of Diseases (ICD), it was defined as death from cardiac disease occurring within 1 hour after onset of symptoms. A total of 2,203 individuals were identified who presumably died of sudden cardiac death outside of

From the Klinikum Steglitz, Free University of Berlin (S.N.W., H.R.A.); the Institute for Prevention of Cardiovascular Disease, Deaconess Hospital, Harvard Medical School, Boston (S.N.W., M. Maclure, M. Mittleman, J.E.M.); and the Harvard School of Public Health, Boston (M. Maclure, M. Mittleman).

Address for correspondence: Stefan N. Willich, MD, MPH, Department of Medicine, Klinikum Steglitz, Free University of Berlin, Hindenburgdamm 30, D-1000 Berlin 45, FRG.

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In both of these studies of time of day of sudden cardiac death, the circadian pattern was similar in subgroups of patients categorized with respect to sex and age.6,7

Arntz et al13 reported preliminary findings on the time of day of sudden cardiac death categorized by out-of-hospital ECG recordings obtained by emergency physicians. Subjects demonstrating an initial rhythm of ventricular tachycardia or fibrillation showed a marked circadian variation in occurrence, whereas those whose initial finding was electromechanical dissociation or asystole were rather evenly distributed throughout the day. Also, younger patients (<45 years old) demonstrated a peak of ventricular fibrillation in the afternoon, whereas older patients had a peak during the late morning.

Hausmann et al14 presented preliminary observations that the circadian variation of ventricular tachycardia in patients with coronary artery disease results primarily from an increased morning risk of arrhythmia in patients with poor left ventricular function (ejection fraction <40%) or long tachycardia duration (>15 beats), i.e., in patients at increased risk of sudden cardiac death. Similarly, patients with arterial hypertension were reported by Zehender et al11 to experience ventricular arrhythmias and ECG changes suggestive of myocardial ischemia more frequently during the morning than at other times of day.

Time of year also appears to influence the frequency of disease onset. There is a 20% increase of cardiac mortality (which is primarily sudden cardiac death) during the months of the climatic winter in the United States (November to February) and in Australia (June to September).37 Similar results have been reported for Kuwait and Scotland.38 Both diurnal and annual patterns of disease onset suggest that the activity of the subjects and external events play roles in triggering disease onset.

Wake-Time Adjustment

The well-documented morning increase of sudden cardiac death raises the question of the timing of disease onset in relation to waking. Although only limited data are available for sudden cardiac death, answers are available for the related conditions of myocardial infarction and transient myocardial ischemia. The results of two studies have now demonstrated a correlation between individual wake time and onset of nonfatal myocardial infarction.39,40 Both studies use a similar design, obtaining information in standardized interviews with patients shortly after myocardial infarction. After adjustment for the individual wake time of the patients, the relative risk of myocardial infarction was approximately threefold during the initial hours after awakening and arising. Also, transient myocardial ischemia has been documented to be markedly increased during the initial 2 hours after awakening.41

The morning increase of onset of sudden cardiac death in the Massachusetts population tended to be delayed on weekends compared with weekdays, suggesting a relation between risk of sudden cardiac death and wake time, which is usually later on weekends. However, wake-time data were not available for that population. Peters et al41 reported preliminary findings that sudden death of 37 patients enrolled in CAST began most frequently within 2 hours after awakening.
Heart Attack Trial (BHAT) demonstrated that propranolol not only reduced the total number of sudden cardiac deaths but also attenuated the morning increase of its occurrence. The beneficial effect of \( \beta \)-adrenergic blockade was concentrated in the hours from 2 AM to 2 PM (Figure 3). Similar findings have been observed in patients with nonfatal myocardial infarction who were treated with \( \beta \)-blockers. It appears possible, therefore, that \( \beta \)-adrenergic blocking agents exert their well-documented beneficial effect in reducing the risk of sudden cardiac death at least in part by inhibiting the triggering mechanisms responsible for the excess risk of the event during the morning. A recent analysis of the CAST data, in contrast to the findings with \( \beta \)-blockade, demonstrated no alteration of the morning peak of sudden deaths in patients treated with encaïnide or flecainide compared with those treated with placebo.

**Activity Preceding Sudden Cardiac Death**

The suddenness of onset of sudden cardiac death, the difficulty of predicting which individual will be affected, and the death of the victim eliminate the possibility of obtaining first-hand historical data of the events in the hours before sudden cardiac death. Only a minority of patients who experience cardiac arrest are resuscitated, and in these, memory of the prior events is often obscure. Few authors have reported the circumstances and events possibly triggering sudden cardiac death. Although some of the studies use the term “sudden death” (rather than sudden cardiac death) because of the uncertainty of an actual cardiac cause of death, a diagnosis of sudden cardiac death is generally assumed if the patient died suddenly in the absence of evidence of a noncardiac cause of death.

**Physical stress.** Some investigations focused on the association between physical activity and onset of sudden cardiac death. Moritz and Zamcheck observed in soldiers during World War II that sudden death of unknown cause frequently occurred during or shortly after strenuous exertion. Thompson et al. compared the incidence of cardiovascular death per man-hour during sedentary activity with the incidence during leisure jogging. From a telephone survey of 510 households in Rhode Island, the investigators inferred that there were 662,000 man-hours of jogging per year in the

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**FIGURE 2.** Bar graph showing wake-time–adjusted analysis of time of sudden cardiac death (SCD) (n=94) in the community. Time of sudden cardiac death demonstrated a circadian variation with an increased incidence during the late morning compared with other times of day (upper panel). Time of sudden cardiac death adjusted for individual wake times demonstrated an increased relative risk of 2.6 (95% CI, 1.6–4.2) during the initial 3 hours after awakening compared with other times of day (lower panel).

A recent study demonstrated similar results in the general population. Ninety-four patients with sudden cardiac death were identified by consecutive review of mortality records in several city halls in Massachusetts, the diagnosis was confirmed, and information on the patients’ wake times was obtained by interviews with family members of the deceased or witnesses of the incident. After adjustment for individual wake times, the relative risk of sudden cardiac death was 2.6 (95% CI, 1.6–4.2) during the initial 3 hours after awakening compared with other times of day (Figure 2).

The wake-time–adjusted findings are compatible with the hypothesis that the circadian variation of sudden cardiac death results primarily from an increased risk during or shortly after the time of awakening and arising. However, determination of the precise relation between time of sudden cardiac death and individual wake times is needed in a larger number of patients to confirm these results. The apparent increase in sudden cardiac death after awakening could be related to the surge in sympathetic activity that accompanies assumption of the upright posture and initiation of activity.

**Influence of Prior Medication on Time of Day of Sudden Cardiac Death**

Cardiac medication before the event has been identified as a modifying factor of the circadian variation of sudden cardiac death. An analysis of the Beta-Blocker

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**FIGURE 3.** Bar graph showing time of sudden cardiac death (SCD) (n=138) in the BHAT study. The patients on placebo had a circadian variation with a marked morning peak. The patients on propranolol had a more even distribution throughout the 24 hours.
entire state. Sudden cardiac death was identified by review of the mortality records and examination of the patients' medical and activity histories. Although there were only 12 recorded cases of sudden cardiac death during jogging during a 6-year period, the age-adjusted relative risk of sudden cardiac death during jogging was estimated to be 7 (95% CI, 4–26) compared with the estimated rate during sedentary activities.

A study in Seattle compared 133 sudden cardiac deaths among married men without a history of heart disease or other chronic disease and a random sample of the healthy population of married men living in the same vicinity. Among men with low levels of habitual activity, the relative risk of sudden cardiac death during vigorous activity was 56 (95% CI, 23–131); among men with high levels of habitual activity, it was 5 (95% CI, 2–14).

Marti et al. reported an incidence of sudden cardiac death during organized mass running events in Switzerland to be 50–1,000 times higher than the incidence expected by chance alone. A comparison of the results of the two latter studies suggests that competitive physical activity carries an even higher relative risk of sudden cardiac death than leisure activity. Several further retrospective analyses of sudden cardiac death during leisure sports, rugby, and cross-country skiing demonstrated a range of observed incidence rates of sudden cardiac death from 0 per 375,000 to 1 per 50,000 man-hours. Although the confidence limits around the estimated risk of sudden cardiac death associated with exertion are wide, in aggregate, these studies suggest that vigorous physical activity in rare instances triggers sudden cardiac death even among relatively fit individuals who engage in sports activities regularly (Figure 4). The incidence data emphasize the extremely low absolute risk of sudden cardiac death during exertion (particularly in regular exercisers) but are compatible with the increased relative risk identified by comparative studies. There remains a lack of data on the risk of sudden cardiac death after moderate physical activity and on the duration of increased risk after a period of strenuous exertion.

Preliminary results of triggering of nonfatal myocardial infarction by exertion are available from two large, controlled studies. Patients were evaluated by standardized questionnaires administered within 2 weeks after myocardial infarction. In the Myocardial Infarction Onset Study, the level of physical activity before the onset of myocardial infarction was compared with the patients' physical activity during the same time interval on the day before the event. This new epidemiological method has been called the case–crossover method, since the subjects cross from control to case status during the transient exposure to exertion. Heavy exertion was reported to be associated with a fivefold increase (95% CI, 2.6–11.1) of risk of myocardial infarction in the subsequent 2 hours. In the Triggers and Mechanisms of Myocardial Infarction (TRIMM) Study, 1,000 patients were frequency-matched to 500 control subjects for age, sex, precinct, and timing of a control event. The patients had a twofold risk (95% CI, 1.2–3.3) of performing exertional physical activities at onset of myocardial infarction compared with the control subjects at onset of the control event.

Mental stress. Previous studies of the role of psychosocial factors in sudden cardiac death have recently been reviewed by Kamarck and Jennings. Determination of the role of mental stress is much more difficult than determination of the role of physical stress because of difficulties inherent in assessing mental stress. Furthermore, many of the investigations of mental stress as a trigger of sudden cardiac death have been hampered by methodological limitations, including the lack of appropriate control data, inadequate measures of psychosocial stress, and a possible systematic reporting bias (e.g., differential recall of more recent mental stress by relatives or close friends of the sudden cardiac death victims).

With these limitations in mind, it is nevertheless important that several retrospective studies have identified an increase in informant-reported life stress either acutely before sudden cardiac death or during the weeks before the event. Myers and Dewar reported in 1975 that in 40 of 100 cases, sudden death occurred within 24 hours after acute psychological stress. Appropriate control data were not presented. Cottington et al. found that sudden cardiac death victims had experienced loss events (death of family member or close friend) six times more frequently than control subjects.

One prospective study using data from BHAT found an association between life stress and social isolation and risk of subsequent sudden cardiac death. However, the measurement of the psychological categories applied in this analysis has been criticized for method-
ological reasons. A correlation of psychological symptoms with risk of sudden cardiac death was also suggested by Frasure-Smith, who reported a significantly lower long-term out-of-hospital death rate for patients after myocardial infarction who participated in a non-specific intervention program essentially based on frequent nursing visits compared with control subjects. Among the control subjects, those with high levels of psychological stress as assessed by a general health questionnaire had a threefold increase in cumulative cardiac mortality compared with control subjects with low levels of psychological stress. This study has also been criticized for methodological difficulties.

In the Cardiac Arrhythmia Pilot Study (CAPS), a higher level of depression, type B behavioral pattern, and low pulse-rate reactivity to challenge were significant predictors of cardiac arrest. In the Recurrent Coronary Prevention Project (RCPP), a type A behavioral pattern was a significant predictor of sudden cardiac death during follow-up of patients after myocardial infarction. Recent preliminary analyses suggested that emotional arousability, a constituent component of type A behavioral pattern, may have an even stronger association with sudden cardiac death than type A behavior (Simon, personal communication).

A “natural experiment” testing the hypothesis that acute stress causes sudden cardiac death was observed by Trichopoulos et al. During the 5 days after the 1981 Athens earthquake, the incidence of death attributable to underlying atherosclerosis rose from the normal average of 2.6 deaths per day to an average of 5.4, with a peak of eight deaths per day. Although psychological stress seems the most likely cause of the excess, it is not possible to exclude a contribution from unusual physical activity, since most of the excess risk was found among men <60 years old, i.e., the sex and age group that would take on the heaviest physical tasks during recovery from the catastrophic event. Similarly, Glass and Zack reported a significant increase (by 22%) from 36.7 to 44.6 deaths per day from ischemic heart disease in eastern Massachusetts during the initial 8 days after six blizzards from 1974 to 1978 compared with preceding and subsequent control weeks. In this situation, it is not possible to isolate the relative roles of physical and mental stress in producing the deaths.

A recent study investigated the effect of mental stress imposed on a population of the incidence of sudden cardiac death. During the initial days of the 1991 Gulf War and after the first missile attack on Israel, a sharp rise in cardiac events was observed in a population of 400,000 individuals living close to Tel Aviv. There were 41 cases of sudden out-of-hospital death during January 1991 compared with 22 cases during the control period 1 year earlier.

Pathophysiological Findings

Coronary Artery Lesions

The majority of patients with sudden cardiac death demonstrate acute lesions of the coronary arteries with underlying atherosclerotic changes. From autopsy data, it is estimated that one third of sudden cardiac deaths are caused by acute total coronary occlusion by thrombus. Clinical findings in resuscitated sudden cardiac death victims corroborate these pathological findings. Episodes of symptomatic or asymptomatic myocardial ischemia with underlying chronic coronary artery disease are associated with increased risk of sudden arrhythmia.

Signs of rupture of an atherosclerotic plaque, which has been demonstrated to be associated with coronary thrombosis, were found in studies by Davies and Thomas in >90% of patients dying of sudden cardiac death, defined in that study as death within 6 hours after onset of symptoms in patients leading a normal life. In 44% of the patients, there was an occlusive (partial or total) intracoronary thrombus, defined as >50% luminal obstruction associated with the site of the plaque rupture. An additional 30% of patients showed evidence of a recent nonobstructive coronary thrombus. Intracoronary thrombi were found to have layered structures, suggesting a history of episodic growth. There was also evidence of peripheral embolization, as demonstrated by occluded intramyocardial arteries distal to the culprit lesion.

At least during the critical phase of plaque rupture and thrombus formation, platelet characteristics and arterial wall function appear to play an important role in the pathogenesis of sudden cardiac death. It has been demonstrated that platelet activation and the release reaction are affected by the presence of acute arterial wall injury, endothelial cell dysfunction, and hemodynamic changes. The subsequent thrombogenic tendency may be enhanced by hypercoagulability caused by reduced function of the fibrinolytic system. Paradoxical coronary vasoconstriction, which has been demonstrated to be a response of diseased arterial vessel walls exposed to acetylcholine, may also predispose to complete occlusion.

Myocardial Tissue Abnormalities

The role of the myocardium in the pathogenesis of sudden cardiac death is still unclear. Patients with ventricular hypertrophy appear to be at a higher risk of sudden cardiac death, although the precise mechanism is still unclear. Hypertrophied rat hearts have been shown to be more susceptible than nonhypertrophied hearts to ventricular fibrillation during acute ischemia.

Myocardial necrosis caused by either proximal coronary occlusion or intramyocardial platelet aggregation and microemboli may also create a substrate for ventricular fibrillation. Animal experiments indicate that one of the mechanisms responsible for the electric instability associated with acute myocardial cell injury may be an acute cytosolic calcium overload. It has been demonstrated that scarred myocardium is associated with electric instability.

Recent controlled studies have revealed ultrastructural abnormalities of the myocardium concentrated in the conduction system in young victims of sudden cardiac death. Signs of intramyocyte virus and subendocardial bacteria have been reported in some cases. These preliminary findings have yet to be confirmed but are consistent with speculation that in isolated cases, as yet unidentified factors may contribute to specific vulnerability of myocardial tissue.

Conduction System Abnormalities and the Causes of Arrhythmia

The conduction system provides the anatomic substrate for an acute cardiac arrhythmia. The possible
ECG triggers of sudden cardiac death include premature beats and bursts of supraventricular or ventricular tachycardia. Triggering of sudden cardiac death by these arrhythmias and triggering of these arrhythmias themselves have been difficult to study. ECG recordings obtained during hospitalization in survivors of sudden cardiac death did not reveal any consistent pattern of cardiac rhythm before spontaneous onset of ventricular tachycardia or ventricular fibrillation.

Different clinical conditions leading to similar arrhythmias and sudden cardiac death have been identified: these include transient hypoxia, electrolyte imbalance, autonomic discharge, and myocardial ischemia. However, a number of patients remain without such possible clinical triggers or any overt cardiac condition who experience sudden cardiac death. As yet unidentified abnormalities of the conduction system may be responsible for such arrhythmic deaths.

Electrophysiological studies that have provided important insight into the arrhythmogenetic pathways have been reviewed in detail recently. However, these studies have not focused on clinical triggers or identified the basic cellular and molecular mechanisms of arrhythmogenesis.

**Autonomic Nervous Activity and Electric Instability**

The role of the autonomic nervous system in triggering arrhythmias has been examined by many investigators. An increase in basal tone or acute stimulation of the central nervous system by drugs or electrical stimuli lowers the threshold for cardiac electric instability and may evoke a variety of arrhythmias, including ventricular fibrillation. Studies in experimental animals have demonstrated a reduced threshold for ventricular fibrillation in dogs subjected to acute psychological stress. Furthermore, overexposure to catecholamines may directly damage myocardial tissue and increase the risk of an arrhythmia.

Recently, in patients who had recovered from ventricular tachycardia or fibrillation, levels of total and cardiac norepinephrine spillover into the plasma were measured several days after the event and were increased relative to matched controls. The authors speculate that depressed ventricular function may lead to increased sympathetic activation producing the arrhythmic events. These findings are consistent with recent evidence that chronic decreases in cardiac sympathetic activation such as those associated with aging may stabilize myocardial electric function. It is, therefore, not surprising that therapeutic left cardiac sympathetic denervation appears to reduce the incidence of tachyarrhythmias and perhaps of sudden cardiac death in patients with long QT syndrome, based on follow-up of 85 patients in 11 countries without a control group.

Many physiological variables possibly involved in triggering sudden cardiac death are closely associated with the function of the autonomic nervous system. Systemic arterial pressure and heart rate, which may influence plaque rupture, rise sharply in response to sympathetic surges. The increase in sympathetic nervous system activity after assumption of the upright posture and triggering activities during the day may acutely lower the arrhythmic threshold. Potassium plasma levels demonstrate diurnal fluctuations that may contribute to electrical imbalance and arrhythmia causation. The relation between platelet activity and sympathetic activity has been investigated in an animal model developed by Fols et al. Cyclic thrombotic plug formation and blood flow changes occur in response to an artificially created coronary stenosis with endothelial cell injury. The thrombotic tendency can be increased by epinephrine infusion and decreased by sympatholytic intervention or nitrate infusion. This model exemplifies the importance of sympathetic activity in the pathogenesis of sudden cardiac death, providing a possible physiological link between physical or psychosocial stressors causing sympathetic activation and the occurrence of fatal arrhythmias.

Analysis of the autonomic control of the heart may, in the future, be used to identify patients at increased risk of sudden cardiac death. Data from animal experiments and preliminary studies of patients after myocardial infarction indicate that depressed baroreflex sensitivity and decreased heart rate variability (both reflecting reduced protective vagal activity) are associated with an increased risk of sudden cardiac death. Nonlinear analysis of beat-to-beat changes of QRS and ST-T morphology, e.g., electric alternans, has been proposed as another new diagnostic method to quantify the association between autonomic function and tendency toward arrhythmia.

**Hypothetical Model of Triggering of Sudden Cardiac Death**

The evidence reviewed above permits formulation of a hypothetical model by which external triggers may cause sudden cardiac death by acting on the coronary artery, myocardial tissue, and the conduction system (Figure 5). The effect begins when an external trigger causes an increase in sympathetic nervous activity. This increase may act on the coronary artery, the myocardial tissue, or the conduction system alone or in various combinations. The effect on the artery occurs when hemodynamic forces cause a "vulnerable" atherosclerotic plaque to rupture. Transformation of a plaque from a stable to a vulnerable state may result from accumulation of a lipid pool covered by a thin fibrous cap, increased collagen activity, and other as yet unidentified processes. In some cases, exposed collagen may lead directly to an intracoronary occlusive thrombus and subsequent fatal myocardial infarction, as has been proposed previously. In other cases, the gradual growth of intracoronary thrombus, depending on the thrombogenicity of the ruptured plaque, the thrombotic tendency of the blood, and the degree of vasocostriction that occurs, may lead to reduced coronary flow, microthrombotic emboli, and subsequent myocardial ischemia or even small areas of myocardial necrosis. Both have been shown to be associated with a reduced threshold for ventricular fibrillation. Damage of myocardial tissue or the conduction system caused by necrosis, fibrosis, hypertrophy, or other changes may increase the risk of acute electric instability.

**Summary**

Epidemiological studies have identified associations between time of day and risk of sudden cardiac death. The marked peak in the occurrence of sudden cardiac death after awakening suggests that the disease is triggered by changes that occur during this time period.
Increased sympathetic stimulation is a likely cause of such triggering. In the light of the circadian variation of sudden cardiac death and the evidence linking physical activity or mental stress (both associated with activation of the sympathetic nervous system) to the disease, the role of potential triggering events should be investigated. Controlled studies are needed to determine the relative risk of activities that may trigger sudden cardiac death. Since such studies must rely on witnesses (or resuscitated patients), data quality must be closely scrutinized, and studies using case-control and case-crossover designs are needed.

The epidemiological and pathophysiological data reviewed in the present article suggest a number of pathways through which activities may trigger sudden cardiac death. Different extrinsic stimuli may cause similar physiological changes that subsequently lead to acute pathological events, a decrease in the ventricular fibrillation threshold through a direct myocardial effect, or a harmful effect on the conduction system. Myocardial ischemia induced by plaque rupture and thrombosis may lead directly to myocardial electric instability. The presence of chronic structural abnormalities of the myocardial tissue or the conduction system may further lower the threshold for electric instability and ventricular fibrillation.

The diversity of the findings provides strong support for the hypothesis that many potential external triggers may interact, synergistically or alone, with structural and functional abnormalities to produce the common clinical end point of sudden cardiac death. The concept that triggering activities may cause sudden cardiac death is not new; it has long been recognized that in exceptional cases a trigger may be present. The new dimension suggested by the evidence reviewed above is that identifiable triggering is relatively common, and unidentifiable triggering by external stressors may occur in the majority of cases.

Much of the research on prevention of sudden cardiac death has focused on prevention during electrophysiological testing of triggering of arrhythmia by electric stimulation. Much has been learned from this approach and from recordings obtained before discharge of automatic implantable cardiac defibrillators. However, there has been relatively little linkage between the knowledge gained from electrophysiological studies and the recent understanding of circadian variation and triggering of disease onset. Application of present electrophysiological recordings to the question of external triggering could lead to greatly improved understanding of the cause of sudden cardiac death. Such knowledge should lead to improved methods of prevention of this catastrophic disorder.

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