

Circadian variation in the frequency of sudden cardiac death

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ABSTRACT To determine whether sudden cardiac death exhibits a circadian rhythm similar to that recently demonstrated for nonfatal myocardial infarction, we analyzed the time of day of sudden cardiac death as indicated by death certificates of 2203 individuals dying out of the hospital in Massachusetts in 1983. The data reveal a prominent circadian variation of sudden cardiac death, with a low incidence during the night and an increased incidence from 7 to 11 A.M. The pattern is remarkably similar to that reported for nonfatal myocardial infarction and episodes of myocardial ischemia. The finding that the frequency of sudden cardiac death is increased in the morning is compatible with hypotheses that sudden cardiac death results from ischemia or from a primary arrhythmic event. Further study of the physiologic changes occurring in the morning may provide new information supporting or refuting these hypotheses, thereby leading to increased understanding and possible prevention of sudden cardiac death.

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ALTHOUGH sudden cardiac death afflicts over 400,000 individuals each year in the United States alone and accounts for approximately 50% of all deaths from coronary artery disease,¹⁻⁴ the mechanisms triggering this common catastrophic event remain obscure. Attempts to identify precipitating mechanisms have been hampered by the rarity of intensive medical observation in the critical moments before its onset. Although frequent in a population, sudden cardiac death is difficult to study because it is impossible to predict in which individual it will occur, and it often occurs without warning in an out-of-hospital setting. Retrieval of physiologic data from those who die is impossible, while in those who are resuscitated, the period of arrest and the techniques of resuscitation obscure the events that preceded the arrest. Of necessity, therefore, our present, limited insight into the mechanism of sudden cardiac death is based primarily on knowledge, gained from extensive epidemiologic and pathologic studies, of predisposing factors.

Such studies indicate that sudden cardiac death frequently occurs in individuals younger than 65 years of age with no prior overt signs of cardiac disease,^{2, 4} and

is most likely to afflict those demonstrating the traditional risk factors for ischemic heart disease.^{4, 5} Pathologic studies have confirmed that sudden cardiac death generally occurs in individuals with extensive coronary atherosclerosis and myocardial damage.^{3, 6} Holter monitoring has demonstrated that ventricular tachycardia degenerating to ventricular fibrillation is often the final event leading to sudden cardiac death,⁷ but the subset of patients undergoing Holter monitoring may not be representative of the larger group experiencing sudden cardiac death, and the mechanisms precipitating the fatal arrhythmia have not been identified.⁸

A new approach to identification of the mechanisms precipitating sudden cardiac death is suggested by the recent demonstration that nonfatal myocardial infarction, an event that is closely associated with sudden cardiac death and shares its unexpected onset, is more likely to occur in the morning than at other times of day.⁹ In addition, episodes of angina at rest,¹⁰ silent myocardial ischemia,¹¹ and the onset of stroke¹² have all been reported to have similar circadian rhythms.

We therefore examined the time of day of sudden cardiac death in 2203 individuals dying in Massachusetts in 1983. The data reveal a circadian rhythm of sudden cardiac death remarkably similar to that observed for nonfatal myocardial infarction, episodes of myocardial ischemia, and stroke. Further characterization of the time of occurrence of sudden cardiac death,

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and the pathophysiologic events that occur at its peak time of onset, may provide new insight into the pathogenesis and means of prevention of this common, lethal disorder.

Methods

Mortality records of the Massachusetts Department of Public Health were used to determine the time of occurrence of sudden cardiac death in a large cohort of individuals. Details on the collection of mortality data by the Commonwealth of Massachusetts have been previously reported.¹³ In brief, the law requires that a death certificate be completed for each person who died in the state. Completed certificates are recorded locally and sent to the central office of the Department of Public Health, where internal consistency checks are performed. A portion of the data on the death certificates is entered into the central computer (Amdahl-5860) of the Department of Public Health.

For the present study, the portions of the death certificates used were the sections describing the age, sex, location of death, date, time of death, interval from onset of symptoms to death, and cause of death as indicated by the physician signing the death certificate. Information on cause of death was obtained from the three-line section on the death certificate asking for designation of the immediate cause of death and two underlying conditions leading to death.

The three conditions listed by the physician completing the form are manually assigned codes by the Department of Public Health using the Ninth Revision of the International Classification of Disease (ICD), adapted for use in the United States.¹⁴ Since there is considerable variation among physicians in the assignment of priority among several conditions related to death, the Department of Public Health uses a computer program developed by the National Center for Health Statistics¹⁵ to apply World Health Organization rules designating which condition should be considered the underlying cause of death. In 37% of cases, the WHO rules alter the physician's assignment of the underlying cause.¹⁶

Identification of the primary analysis group. For the present study, as a first step, it was necessary to identify a large number of individuals dying of sudden cardiac death, defined as death from cardiac disease occurring less than or equal to 1 hr after onset of symptoms. It was decided to conduct the primary analysis on sudden cardiac death occurring out of the hospital (including death on hospital arrival), since out-of-hospital deaths occur in the presence of normal endogenous and exogenous circadian rhythms, which are altered in hospitalized patients. Furthermore, Hinkle and Thaler¹⁷ have noted that "arrhythmic deaths," the focus of the present study, account for 88% of out-of-hospital cardiac deaths, but only 29% of in-hospital cardiac deaths, for which "circulatory failure" was found to be the most frequent cause.

Since previous epidemiologic studies indicate that sudden cardiac death accounts for a substantial portion of total mortality, the overall mortality breakdown for Massachusetts was surveyed as a first step in selecting the primary analysis group (table 1). There were 54,742 deaths in Massachusetts in 1983. Classification by cause of death indicated that diseases of the circulatory system (ICD-390 to ICD-459) were the leading cause of death, accounting for 49% of the total. Ischemic heart disease (ICD-410 to ICD-414) accounted for 30.8% of all deaths. The numbers of deaths assigned to the individual codes of interest are shown in table 1.

The Department of Public Health generated a list of the names and death certificate numbers of the 18,027 individuals whose deaths were classified as ICD-410, ICD-414, or ICD-427

TABLE 1
Classification of deaths

	n	Percent of total deaths ^A
Total deaths in Massachusetts in 1983	54,742	100.0
Diseases of the circulatory system (ICD-390 to ICD-459)	26,798	49.0
Ischemic heart disease (ICD-410 to ICD-414)	16,861	30.8
Acute myocardial infarction (ICD-410)	8,620	15.7
Chronic ischemic heart disease (ICD-414)	8,172	14.9
Cardiac dysrhythmias (ICD-427)	1,235	2.3

^APercentages do not total 100% because only selected ICD codes are presented.

(32.9% of all deaths); the list included the variables age, sex, location of death, and date of death. Since the time of death and the interval from onset of symptoms to death were not routinely entered into the Department of Public Health computer, the death certificates of individuals in these three ICDs who were selected for study were manually reviewed and the times were recorded and entered into a new data file. Comparison of a random sample of 80 (1%) of the times in the new file with the original certificates revealed a recording error in only one case.

The characteristics of the deaths classified as ICD-410, ICD-414, and ICD-427 are presented in table 2. It is apparent that the classification ICD-410, acute myocardial infarction, contains most of the out-of-hospital cardiac deaths occurring an hour or less after onset of symptoms. Therefore, the primary analysis group for determination of the time of occurrence of sudden cardiac death was defined as the group of 2203 individuals whose deaths fell within ICD-410 who died an out-of-hospital death from ischemic heart disease less than or equal to 1 hr after the onset of symptoms.

Other groups of analysis. To determine the time of occurrence of sudden cardiac deaths classified under ICD codes other than ICD-410, we also studied patients listed under ICD-427, "cardiac dysrhythmias" and a random sample of those listed as ICD-414, chronic ischemic heart disease. (All data presented for ICD-414 are multiplied by six to account for a one-sixth sampling fraction.) Only an estimated 685 out-of-hospital sudden cardiac deaths were found in these two categories. Only 102 deaths were classified under the ICD-798, sudden death, cause unknown.

To permit a comparison of the incidence of sudden cardiac death observed in the present study with that previously reported by others, we calculated age- and sex-specific incidence rates for the total sudden cardiac death population identified (i.e., deaths occurring in or out of hospital classified under ICD codes 410, 414, or 427 and known to have occurred, or estimated to have occurred, 1 hr or less after onset of symptoms).

To investigate the possibility that the data from the death certificates underestimated the incidence of sudden cardiac death during the night because deaths during sleep are reported to have occurred at the normal time of awakening, a literature search was conducted to determine the frequency of sudden cardiac death during sleep in previously published detailed epidemiologic studies.

Statistical methods. To quantify the periodic structure of the frequency of occurrence of sudden cardiac death, single-harmonic regression models were fitted to the data. Since the pattern of occurrence of sudden cardiac death suggested bimodality, a two-harmonic regression model was also fitted to the data.

TABLE 2
Timing and characteristics of deaths

ICD category	Number of deaths	Time of death reported	Interval ^A ≤4 months	Out-of-hospital death	Interval ≤24 hr	Interval ≤1 hr	Interval ≤10 min
Acute myocardial infarction (ICD-410)	8620	8230	6637	2633	2535	2203 ^B	1942
Chronic ischemic heart disease (ICD-414)	8172	7512	1543	634	516	451	399
Cardiac dysrhythmias (ICD-427)	1235	1199	841	255	246	234	203

^AReported interval from onset of symptoms to death.

^BDesignated the primary analysis group.

The period of the oscillation was taken to be 24 hr. Model goodness of fit was evaluated by *t* tests (two-tailed) on the estimated coefficients, *F* tests on the overall model, and *R*² and adjusted *R*² statistics.^{18, 19}

Results

Primary analysis group. The time of day of sudden cardiac death of individuals in the primary analysis group is shown in figure 1. A statistically significant (*p* < .01) circadian rhythm is evident, with a primary peak from 10 to 11 A.M. and a secondary peak from 5 to 6 P.M. There is a strong similarity between this circadian rhythm of sudden cardiac death and the previously reported circadian rhythm of nonfatal myocardial infarction⁹ (figure 2).

Characteristics of patients whose deaths were classified in ICD-410 and who were excluded from the primary analysis group because of missing data were analyzed to assess the possibility that the primary analysis

group was a biased subset of ICD-410 deaths. A total of 1593 of the 8620 individuals in the ICD-410 group were excluded from the primary analysis group because the interval from onset of symptoms to death was not reported, or was reported to be greater than 4 months, although time of death was reported. The time of day of cardiac death in this group demonstrated a circadian rhythm parallel to that in the primary analysis group.

Although 390 additional individuals were excluded from analysis because their time of death was not reported, in 283 of these, the physician indicated on the death certificate that the interval from onset of symp-

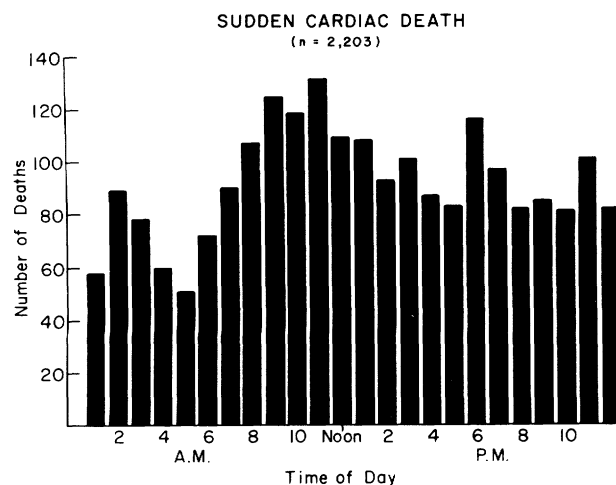


FIGURE 1. The time of day of out-of-hospital sudden cardiac death (ICD-410, ≤ 1 hr from onset of symptoms to death) for 2203 individuals dying in Massachusetts in 1983. A statistically significant (*p* < .001) circadian rhythm is present with a primary peak between 7 and 11 A.M. and a secondary peak between 5 and 6 P.M.

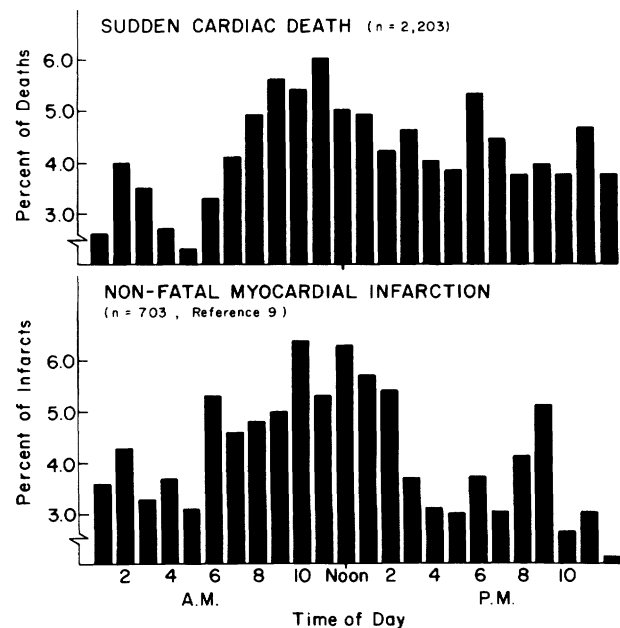


FIGURE 2. A comparison between the circadian rhythm of sudden cardiac death and the previously reported⁹ circadian rhythm of nonfatal myocardial infarction. The percent of total events occurring during each hour of the day for the 24 hr period is plotted. Both rhythms show a trough during the night (midnight to 4 A.M.), a primary peak between 6 A.M. and noon, and a secondary peak between 5 and 9 P.M.

toms to death was 1 hr or less. This level of information suggests that the omission of the time of death was more likely due to a clerical error than to a selective lack of observation during the night. Finally, there were 75 individuals (0.9%) whose deaths fell in the ICD-410 category for whom neither interval from onset of symptoms to death nor time of death was reported. Assumption that all of these deaths occurred from 11 P.M. to 6 A.M. did not abolish the low frequency of sudden cardiac death during the night.

A statistically significant circadian rhythm similar to that observed for the group as a whole was also observed for men and women, and for the older and younger halves of the population.

Other groups of analysis. Review of the time of occurrence of the estimated 685 out-of-hospital sudden cardiac deaths attributed to chronic ischemic heart disease (ICD-414) and to cardiac dysrhythmias (ICD-427) revealed that the sudden cardiac deaths in these categories also demonstrated a circadian rhythm similar to that shown in figure 1.

To eliminate a potential influence of errors in the determination of the interval from onset of symptoms to death, and of errors in assignment to the three codes, an analysis of time of death was conducted, regardless of the interval from onset of symptoms to death, for ICD codes 410, 414, and 427 combined. For out-of-hospital cardiac deaths there was a prominent circadian rhythm similar to that observed for the primary analysis group (figure 3). For the in-hospital deaths (figure 4), the likelihood of occurrence of cardiac death was almost randomly distributed over the 24 hr of the day.

The sudden cardiac deaths identified in the present

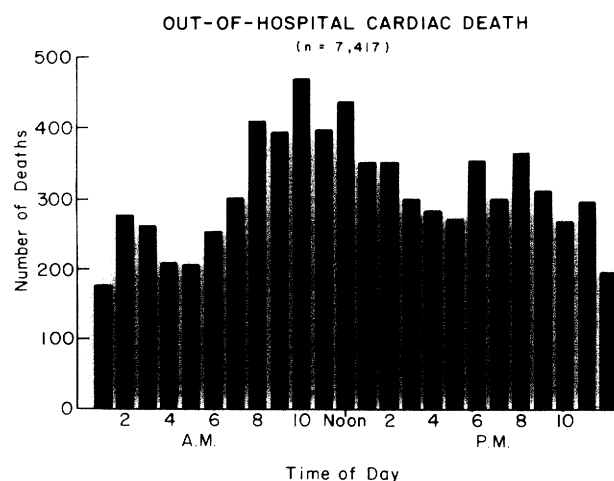


FIGURE 3. The time of day of out-of-hospital cardiac death (ICD codes 410, 414, 427), regardless of the interval from onset of symptoms to death, for 7417 individuals dying in Massachusetts in 1983. A statistically significant ($p < .001$) circadian rhythm is present with a primary peak from 7 to 11 A.M.

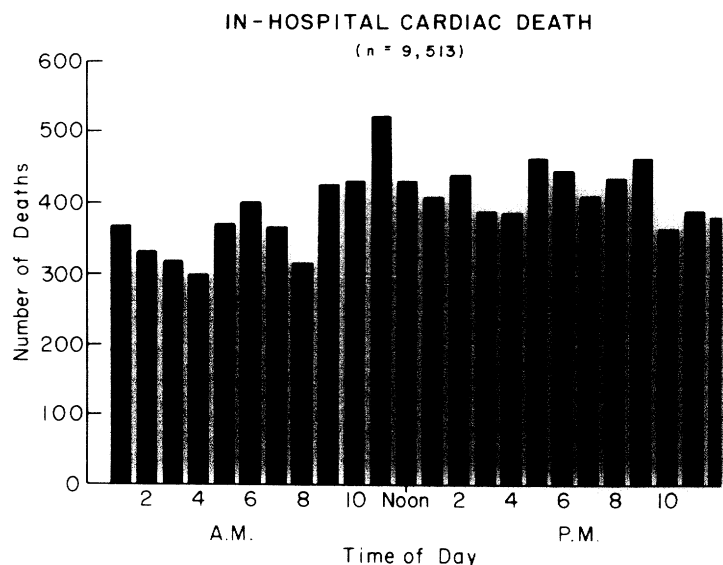


FIGURE 4. The time of day of in-hospital cardiac death (ICD codes 410, 414, 427), regardless of the interval from onset of symptoms to death, for 9513 individuals dying in Massachusetts in 1983. For these hospitalized patients, the time of cardiac death is almost randomly distributed over a 24 hr period, although there is a tendency toward fewer deaths in the period from midnight to 6 A.M.

study accounted for 10.1% of all deaths in Massachusetts in 1983. Age- and sex-specific incidence rates were similar to those obtained in previous population-based studies of sudden cardiac death.

Results of the review of previous studies to determine the frequency of sudden cardiac death during sleep are presented in table 3.^{17, 20-25} Only 85 of the 689 patients studied experienced sudden cardiac death during sleep. This 12.3% incidence during sleep is significantly ($p < .001$) below the 29% that would be expected if the time of occurrence of sudden cardiac death were randomly distributed throughout a 24 hr period with a 7 hr period of sleep.

TABLE 3
Incidence of sudden cardiac death during sleep

Study	Number of deaths	Deaths during sleep n	(%)
Bean ²⁰	88	16	18
French and Dock ²¹	80	8	10
Moritz and Zamcheck ²²	115	15	15
Myers and Dewar ²³	100	9	9
Baroldi ²⁴	208	22	11
Hinkle and Thaler ¹⁷	82	12	15
Roelandt et al. ^{A 25}	16	3	19
Total	689	85 ^B	(12.3)

^ATime of death determined by Holter monitoring.

^B $p < .001$ vs the 201 (29%) expected if sudden cardiac death were randomly distributed over a 24 hr period with 7 hr of sleep.

Statistical assessment of circadian rhythmicity of sudden cardiac death. All regression fits to the three sets of data were statistically significant as assessed by F tests, indicating the periodic nature of sudden and nonsudden cardiac death. For the primary analysis group, the one-harmonic fit to the data was statistically significant (F test, $p < .01$). For this model, the estimated coefficient for the cosine term was significantly different from zero (t test, $p < .01$), while the coefficient of the sine term was statistically indistinguishable from zero. The R^2 and adjusted R^2 for this model were 43.3% and 37.9%, respectively.

The single-harmonic regression equation for the frequency of sudden cardiac death in the primary analysis group is as follows:

$$\text{Sudden cardiac deaths per hour} = 91.8 - 18 \cos \frac{2\pi t}{24} - 5.1 \sin \frac{2\pi t}{24}$$

where t = time of day in hours. The two-harmonic regression equation for the frequency of sudden cardiac death is:

$$\begin{aligned} \text{Sudden cardiac deaths per hour} = \\ 91.8 - 18.0 \cos \frac{2\pi t}{24} - 5.1 \sin \frac{2\pi t}{24} + \\ 7.7 \cos \frac{4\pi t}{24} - 11.7 \sin \frac{4\pi t}{24} \end{aligned}$$

Although the coefficient of the second harmonic cosine term was not statistically significant (t test, $p > .5$), the coefficient of the second harmonic sine term was (t test, $p < .01$), indicating the value of the second harmonic. This two-harmonic equation demonstrated an improved fit to the data (F test, $p < .01$). There was a 24.3% improvement in the R^2 and a 22.8% improvement in the adjusted R^2 as compared with the single-harmonic fit to the same data. There was also a significant improvement in the fit of the regression model to the data from the in-hospital and out-of-hospital cardiac death groups when a second harmonic was added.

Discussion

The data obtained demonstrate a prominent circadian rhythm in the frequency of sudden cardiac death, with a low frequency during the night and a peak frequency of occurrence from 7 to 11 A.M. This rhythm is remarkably similar to that recently demonstrated for the frequency of onset of nonfatal myocardial infarction,⁹ the recognition of which provided the impetus for the present study. A similar circadian rhythm is present for the larger group of individuals dying out of the hospital from cardiac disease (sudden and nonsud-

den) classified under any of the three ICD codes studied. For those who died in-hospital, the hourly frequency of death from cardiac disease is almost equal, as might be expected in a setting in which daily variations in activity are markedly reduced.

Death certificates, which provided data for the present study, are known to have serious inadequacies, especially with regard to accuracy of determination of cause of death.^{26, 27} Such inadequacies of death certificates were not insurmountable obstacles to the present study for several reasons. First, our study was not primarily an attempt to define the incidence of sudden cardiac death in a community — our goal of studying the time of occurrence of sudden cardiac death required only that a large number of cases of sudden cardiac death with known time of onset be identified. Second, although death certificate diagnoses of specific causes of death are unreliable, general categories such as death from ischemic heart disease are reliable.^{28, 29} The use of such larger categories (ICD-410, ICD-414, and ICD-427 combined), together with the requirement that death should have occurred 1 hr or less after onset of symptoms, permitted identification as sudden cardiac deaths a group of deaths occurring with approximately the same frequency, age distribution, and sex distribution as sudden cardiac deaths identified by community-based studies.³⁰⁻³² Finally, the study relied primarily on time-of-death data, which have not been the object of the same criticism that have cause-of-death data, although a number of potential biases were considered and found not to account for our results.

There are a number of previous reports of the frequency of sudden cardiac death during sleep that provide an unbiased estimate of the likelihood of its occurrence during the night. Review of these studies^{17, 20-25} as presented in table 3 indicates that only 12.3% of these deaths occurred during sleep, a number significantly below the 29% expected if sudden cardiac death were randomly distributed over a 24 hr day with 7 hr of sleep. This finding provides independent support for a low frequency of sudden cardiac death from 11 P.M. to 6 A.M., which is a prominent feature of the circadian rhythm observed in the present study.

In addition to the variation observed during the period from 9 P.M. to 9 A.M., there is a marked decrease in the frequency of out-of-hospital sudden cardiac death from 11 A.M. to 5 P.M., and a secondary peak from 5 to 6 P.M. During these daytime hours, the reliability of ascertainment of the time of death and determination of the cause of death is likely to be constant.

It is more likely that the limitations of the present

data lead to an underestimate, rather than an overestimate, of the magnitude of the circadian rhythm of the dominant process causing sudden cardiac death. In the absence of confirmation of cause of death by autopsy, there are undoubtedly a number of individuals classified as dying of sudden cardiac death who die of non-cardiac causes.^{26, 27} These causes may lack a circadian rhythm of occurrence, or may have a circadian rhythm differing from that of the dominant cause of sudden cardiac death. Inclusion of such cases would tend to obscure the circadian rhythm of the dominant cause of sudden cardiac death.

Even within the group of patients correctly identified as dying from the syndrome of sudden cardiac death, there may be several different causes with competing circadian rhythms. A competing rhythm from a parasympathetically mediated cause of sudden cardiac death during sleep in a subset of cases could tend to obscure the circadian rhythm of the process in which ventricular tachycardia precedes sudden cardiac death.³³

Finally, data about the waking time of the individuals or the prevalence of abnormal wake-sleep cycles were not available for the individuals in the present study. Recalculation of hourly frequencies of sudden cardiac death adjusted for time of awakening would be likely to yield a more prominent circadian rhythm.

There are a number of prior studies of time of death that support the conclusion of the present study, although none feature its combination of size and specificity of diagnosis. In a summary report of 432,892 deaths from 49 separate studies, Smolensky *et al.*³⁴ reported a circadian rhythm for total mortality, with a peak at 6 A.M. In a subgroup of 7644 individuals in whom death was reported to be due to a cardiovascular cause, there was a significant circadian rhythm with a peak at 10 A.M. Mitler *et al.*³⁵ demonstrated a circadian rhythm for total mortality in a study of 4619 deaths in New York State. The rhythm for total mortality was generated by a circadian rhythm of ischemic heart disease mortality, which peaked at 8 A.M. Finally, a study from the German Democratic Republic demonstrated a similar rhythm for out-of-hospital cardiac mortality.³⁶

The finding that sudden cardiac death has a circadian variation similar to that of nonfatal myocardial infarction is of interest because of the uncertain relationship between the two disorders. Signs of myocardial infarction or ischemia are often observed in individuals resuscitated from sudden cardiac death (in 45% to 78% of cases),^{37–39} but it is unclear whether the ischemia and infarction contribute to, or result from, the arrhythmic event. Several observations from Holter monitoring

indicate that ischemic ST segment deviations precede the appearance of lethal arrhythmias,^{40, 41} but the finding is not universal and the group monitored may be a biased subset. A close linkage between sudden cardiac death and myocardial infarction has been suggested by their common risk factors,^{2, 4, 5} the similar degrees of coronary atherosclerosis accompanying them,^{3, 6} and the parallel reductions in incidence of myocardial infarction and sudden cardiac death resulting from therapy with either aspirin^{42, 43} or β -adrenergic blockers.⁴⁴

There are several possible explanations for the remarkable similarity between the circadian rhythms of sudden cardiac death and nonfatal myocardial infarction. The two disorders may have a common antecedent process that is more likely to occur in the morning, they may have separate antecedent processes, each of which is more likely to occur in the morning, or myocardial infarction may be a more frequent cause of sudden cardiac death than is currently recognized.

The observation that sudden cardiac death is more likely to occur from 7 to 11 A.M. is compatible with the two leading theories of causation of this disorder. First, there are extensive data supporting the hypothesis that most cases of sudden cardiac death are a consequence of myocardial ischemia.⁴⁵ The hypothesis has been advanced that sudden cardiac death results from ischemia secondary to the formation of platelet aggregates on an atherosclerotic coronary lesion.⁴⁶ This process could well be more likely to occur in the morning since it is a time of rising arterial pressure,⁴⁷ which may increase the likelihood of rupture of an atherosclerotic plaque, thereby exposing thrombogenic collagen,⁴⁸ increasing coronary artery tone,⁴⁹ and increasing platelet aggregability.⁵⁰ Second, it has been proposed that in a number of cases sudden cardiac death is the result of a primary arrhythmic event.⁵¹ Such a fatal arrhythmia might be more likely to occur in the morning since increased activity of the sympathetic nervous system at that time⁵² may increase electrical instability.⁵³

Thus, the morning appears to be a time when the “transient risk factors”¹ that lead to sudden cardiac death are likely to be prominent. Further studies of the physiologic changes that occur during the vulnerable morning period may provide additional insight into the mechanism of sudden cardiac death and suggest possible means of prevention.

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