Circadian Variation of Sudden Cardiac Death Reflects Age-Related Variability in Ventricular Fibrillation

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Background. Previous studies report a morning peak in the occurrence of out-of-hospital sudden cardiac death but lack detailed information on underlying arrhythmias. We used the documentation system of the semiautomated defibrillators used by emergency medical technicians to investigate the circadian pattern of defined arrhythmias and the influence of demographic patient characteristics on this pattern.

Methods and Results. From December 1988 to December 1990, 703 consecutive patients (63% men; age, 67±17 years) with sudden cardiac death were registered in the Klinikum Steglitz area of the Berlin emergency care system. Determination of time of day of the event was based on the arrival time of the rescue squad. A marked circadian variation (P<.0001) in the occurrence of sudden cardiac death was observed with a primary morning peak (6 AM to noon) and a secondary afternoon peak (3 to 7 PM). The subgroup of 294 patients with ventricular fibrillation as initially documented arrhythmia showed a similar circadian variation (P<.0001). In significant contrast (P<.01), patients with asystole (n=260) or pulseless bradycardia (n=149) were more evenly distributed during the daytime with a primary night trough. Multivariate logistic regression analysis revealed that the circadian pattern of ventricular fibrillation was similar in both gender groups but tended to differ with regard to age: patients older than 65 years demonstrated a monophasic distribution, whereas patients aged 65 years or less had a biphasic distribution with peaks in the morning and in the afternoon.

Conclusions. The circadian pattern of sudden cardiac death reflects primarily a circadian variation in onset of ventricular fibrillation. The different circadian patterns of ventricular fibrillation, pulseless bradycardia, and asystole suggest different pathophysiological mechanisms of causation of death. The age dependence of the pattern of ventricular fibrillation may indicate different underlying external or endogenous triggers. (Circulation. 1993;88[part 1]:2284-2289.)

Key Words • sudden cardiac death • fibrillation • circadian rhythm • aging • defibrillators

A characteristic circadian variation of out-of-hospital sudden cardiac death with a peak incidence during the morning hours between 6 AM and noon has been reported.1-4 Differences in circadian variation of arrhythmia precipitating sudden cardiac death could provide insight into specific mechanisms triggering sudden cardiac death. However, data on underlying arrhythmias were not routinely obtained in these prior studies. We therefore used arrhythmia documentation by tape recordings in automated external defibrillators (AED) used by emergency medical technicians during resuscitation attempts to determine the circadian pattern of particular arrhythmias underlying sudden cardiac death and the influence of demographic patient characteristics on this pattern.

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Methods

Study Population and Data Collection

From December 1988 to December 1991, an evaluation was performed of all consecutive tape recordings obtained by emergency medical technician-initiated resuscitation attempts that occurred in the area of our institution (330,000 individuals, one sixth of the former West Berlin population living in an area of about 100 km²).

In Berlin, rescue services are by law coordinated by the fire department. The emergency medical system usually answers to patient- or bystander-initiated phone calls to the emergency phone number 112. The first tier of the two-tiered Berlin emergency medical system is formed by emergency medical technicians (EMTs) — firefighters with additional training who have used AEDs (LP 200 Physio-Control, Redmont, Wash) routinely during resuscitation attempts since December 1988. The second tier is formed by hospital-based, emergency physician-staffed mobile intensive care units that are alerted in life-threatening situations according to a key word catalogue. The key words are unconsciousness (about 40% of the resuscitation attempts), chest pain (20%), respiratory distress (25%), severe bleeding, shock, and severe injury.

For the purpose of the present study, sudden cardiac death was defined as sudden unexpected nontraumatic
TABLE 1. Demographic Data, Underlying Disease, and Time Intervals From Collapse or Alarm to Rhythm Registration in 703 Patients With Resuscitation Attempts

<table>
<thead>
<tr>
<th></th>
<th>Ventricular Fibrillation (n=294)</th>
<th>Bradyarrhythmias (n=149)</th>
<th>Asystole (n=260)</th>
<th>Total (n=703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±14</td>
<td>70±17</td>
<td>65±19</td>
<td>67±17</td>
</tr>
<tr>
<td>Men, %</td>
<td>68</td>
<td>55</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Underlying cause of arrhythmia*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary arrhythmia, %</td>
<td>52</td>
<td>19</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>46</td>
<td>25</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>Intoxication, %</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unclear, %</td>
<td>0</td>
<td>50</td>
<td>47</td>
<td>20</td>
</tr>
<tr>
<td>Time delay from collapse to rhythm registration, min</td>
<td>11.1±5.0</td>
<td>13.2±6.6</td>
<td>16.7±9.8</td>
<td>13.3±7.5</td>
</tr>
<tr>
<td>Time delay from alarm to rhythm registration, min</td>
<td>8.3±1.8</td>
<td>8.4±2.0</td>
<td>8.5±2.0</td>
<td>8.4±2.0</td>
</tr>
</tbody>
</table>

*Information available only for patients subsequently hospitalized and stabilized (148 patients with ventricular fibrillation, 25 with bradyarrhythmia, and 22 with asystole).

†Information available for 435 patients.

depth in adults. These patients generally collapsed shortly before alarm or arrival of the rescue team. Therefore, initiation of resuscitation measures appeared reasonable to the first-arriving rescue squad. Time intervals between alarm and ECG registration by the EMTs were routinely recorded. The delay from collapse to ECG registration was estimated by the emergency physician based on witness reports or circumstantial evidence.

Rhythm Analysis

The AED continuously registers the rhythm of the victim by patch electrodes on one channel of the built-in tape recorder. On the other channel, the voices of the rescue personnel are taped. After each resuscitation attempt, the tape including additional information on observations on arrival and during the resuscitation is sent to our hospital. The tapes and medical records are evaluated by experienced emergency physicians (cardiologists). Arrhythmia analysis is based on the ECG printouts of the rhythm registered during the first period of analysis by the AED. The analysis period, which is completely displayed in the event report, lasts minimally 6 seconds (in case of ventricular fibrillation) and maximally 12 seconds (in case of asystole). The specificity of the analysis algorithm with regard to the identification of ventricular fibrillation has been estimated to be 99% and the sensitivity to be more than 91%.5 In case of ventricular fibrillation with an amplitude of <0.1 mV with pacemaker spikes or pseudorhythmic ventricular fibrillation with frequencies <180/ min, ventricular fibrillation is not detected by the algorithm of the AED. Movement artifacts, for example, those caused by manipulation of the patient during the analysis phase, are recognized by the AED by continuous measurement of impedance and lead to interruption of the automatic rhythm analysis. Each tape was manually reviewed and corrected if necessary to avoid misinterpretations of the computerized evaluation program delivered by the manufacturer of the AED. Also, 10% of the recordings were independently checked by a second examiner. Arrhythmias were categorized into ventricular fibrillation, asystole, and pulseless bradyarrhythmias.

Statistics

The circadian variability of events was tested for equal distribution using the x^2 goodness-of-fit test. Data were compiled in four 6-hour intervals (0.01 h until 6.00 h, 6.01 h until 12.00 h, 12.01 h until 18.00 h, and 18.01 h until 24.00 h). These intervals were chosen on the basis of data from prior studies on the circadian variation of sudden cardiac death.1-6 Age distribution and time intervals were compared by the Mann-Whitney test. Multivariate logistic regression analysis was performed including the variables of rhythm, sex, and age. A P value of <.05 was considered to be significant if not indicated differently.

Results

From December 1988 until December 1991, 703 resuscitation attempts were performed by EMTs using the AED in patients with sudden cardiac death (63% men; age, 67±17 years; range, 18 to 100 years). Fifty-two percent of the collapses were documented eyewitnessed events. Among the first recorded arrhythmias, 294 were ventricular fibrillation, 260 were asystole, and 149 were pulseless bradyarrhythmias. Information on the age- and sex-specific distribution in the arrhythmia groups is presented in Table 1. Twenty-four of the asystolic patients (9%), 40 of the patients with pulseless bradyarrhythmia (27%), and 162 of the patients with ventricular fibrillation (55%) had successful on-site resuscitations and arrived alive at an intensive care unit. Fig 1 shows the circadian variation (P<.0001) of resuscitation attempts of all 703 patients reviewed in our study. The incidence sharply increases at 6 AM and reaches a maximum 4 hours later. After a short decline, there is a secondary peak between 3 and 7 PM. With respect to the different arrhythmias underlying nontraumatic sudden death (Fig 2), patients with ventricular fibrillation demonstrated a primary morning peak between 6 AM and noon and a second peak during the afternoon hours. In significant contrast to this pattern...
(P<.01), patients with pulseless bradyarrhythmias or with asystole were more equally distributed over the day. However, patients with bradyarrhythmias or asystole also exhibited a significant circadian variation, which appears to result primarily from a night trough. Information on the number of patients, χ² values, and P values for patient groups categorized with regard to time of day, arrhythmia, sex, and age is presented in Table 2.

Age tended to influence the diurnal variation of ventricular fibrillation (Fig 3). Whereas patients older than 65 years had a monophasic pattern with a pronounced morning peak, younger patients had an additional second peak during the afternoon. Both men and women exhibited a similar biphasic circadian pattern of sudden cardiac death with a primary morning maximum and a second minor peak during the afternoon.

Multivariate regression analysis included age (≤65 versus >65 years), sex, arrhythmia, and time of day (night: 00.01 to 6.00) versus morning (6.01 to 12.00) versus afternoon (12.01 to 18.01) and evening (18.01 to 24.00). Compared with the night interval, a significant influence on the morning interval was demonstrated for ventricular fibrillation (P=.002; odds ratio, 2.9; 95% confidence interval, 1.5 to 5.7) and older age (P=.0027; odds ratio, 2.1; 95% confidence interval, 1.2 to 3.8). A similar influence of ventricular fibrillation and older age was demonstrated comparing night and afternoon intervals. There was no significant influence by any of the variables comparing the night and evening intervals.

There were no differences in time delay from alarm to ECG registration among the different types of arrhythmias (Table 1). However, the estimated intervals from collapse to ECG registration were significantly larger for asystole compared with bradyarrhythmia (P<.02) and with ventricular fibrillation (P<.001) and for bradyarrhythmia compared with ventricular fibrillation (P<.03).

Information on the diseases precipitating sudden cardiac death was obtained from all patients subsequently hospitalized and stabilized (Table 1). To exclude a possible influence selection bias caused by EMTs, we compared the diurnal variation in patients declared dead on arrival and where no resuscitation was attempted with those where a resuscitation was initiated by the rescue squad. Both patient groups demonstrated a similar circadian pattern of events (Fig 4).

**Discussion**

In several studies, a marked circadian variation in the incidence of sudden cardiac death has been described.1-4 These reports, however, were based on retrospective analysis of death certificates, autopsy reports, and/or interviews with eyewitnesses or relatives of the
Table 2. Circadian Variation in Patient Groups Categorized With Regard to Arrhythmia, Sex, and Age

<table>
<thead>
<tr>
<th></th>
<th>Time of Day</th>
<th></th>
<th></th>
<th></th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-6, %</td>
<td>6-12, %</td>
<td>12-18, %</td>
<td>18-24, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation (n=294)</td>
<td>5</td>
<td>42</td>
<td>37</td>
<td>16</td>
<td>65.1</td>
<td>.0001</td>
</tr>
<tr>
<td>Bradyarrhythmia (n=149)</td>
<td>10</td>
<td>34</td>
<td>30</td>
<td>26</td>
<td>12.1</td>
<td>.007</td>
</tr>
<tr>
<td>Asystole (n=260)</td>
<td>14</td>
<td>32</td>
<td>27</td>
<td>27</td>
<td>10.2</td>
<td>.016</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=443)</td>
<td>10</td>
<td>36</td>
<td>30</td>
<td>24</td>
<td>38.9</td>
<td>.0001</td>
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<tr>
<td>Female (n=260)</td>
<td>8</td>
<td>37</td>
<td>35</td>
<td>20</td>
<td>34.3</td>
<td>.0001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>&gt;65 y (n=426)</td>
<td>8</td>
<td>39</td>
<td>32</td>
<td>21</td>
<td>56.8</td>
<td>.0001</td>
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<tr>
<td>≤65 y (n=277)</td>
<td>12</td>
<td>32</td>
<td>31</td>
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<td>17.6</td>
<td>.0005</td>
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<tr>
<td>Total (n=703)</td>
<td>9</td>
<td>36</td>
<td>32</td>
<td>22</td>
<td>71.5</td>
<td>.0001</td>
</tr>
</tbody>
</table>

deceased. Although ventricular fibrillation is the most common arrhythmia precipitating sudden cardiac death,7 to our knowledge, no data are available on the influence of specific arrhythmias on the circadian pattern of the disease. Furthermore, most reports on the role of ventricular fibrillation as the cause of sudden cardiac death were based on selected study populations or were derived from studies investigating different approaches to improve out-of-hospital resuscitation results.8-11 Thus, information obtained from tape recordings in AEDs during resuscitation attempts in an unselected population appeared to be an ideal source of information on arrhythmias underlying sudden cardiac death.

Our study confirms prior findings of a biphasic circadian pattern in the incidence of sudden non-
traumatic death, which is primarily sudden cardiac death. In the case of ventricular fibrillation as the precipitating arrhythmia, death is almost exclusively due to a cardiac cause. Therefore, it is not surprising that circadian variation in the incidence of ventricular fibrillation parallels the biphasic curve of incidence of sudden death in the whole study population. Bradycardia and asystole were more evenly distributed. It is of note that the missing morning peak in asystolic patients excludes the possibility that persons found dead in the morning (ie, unwitnessed cardiac arrest during the night hours) could have influenced the morning peak of events in the total study population. The time lag between collapse and resuscitation may be of importance in interpreting the influence of patients found in asystole on circadian variations of sudden cardiac death. It is possible that some of the patients found in asystole may have had ventricular fibrillation as the initial arrhythmia only a few minutes before arrival of the rescue personnel. Adding these patients to the group of ventricular fibrillation would only attenuate the relative extent of the circadian pattern but not the absolute differences in magnitude, since asystole also demonstrated a significant circadian pattern. The similarity in circadian variation of individuals in whom resuscitation was initiated compared with those declared dead without resuscitation attempts renders a possible bias caused by selection of EMTs very unlikely.

The circadian pattern of sudden cardiac death coincides with the variation in the onset of acute myocardial infarction and stroke.12-15 In our study, about 50% of the survivors of ventricular fibrillation had clinical evidence of acute myocardial infarction. This is compatible with prior autopsy findings indicating that 30% to 50% of sudden cardiac death is caused by acute myocardial infarction.16,17 Possible underlying pathophysiological mechanisms of the circadian variation of sudden cardiac death, acute myocardial infarction, myocardial ischemia, and stroke include acute changes in catecholamine levels, platelet aggregability, fibrinolytic activity, blood viscosity, and coronary tone.18-21 It has been proposed that mental stress, unusual physical exertion, or physical stress associated with awakening and arising may trigger the onset of acute cardiovascular disease.19,22 It is unclear whether these mechanisms may directly precipitate fatal arrhythmias or induce arrhythmias via myocardial ischemia or other modifying factors such as electrolyte imbalance or biochemical or structural alterations of the myocardium. The similar circadian pattern for sudden cardiac death and myocardial infarction18 supports the concept of a direct relationship. The lack of influence of age on the circadian pattern of acute myocardial infarction in several studies may at least in part be due to study-inherent selection mechanisms, eg, exclusion of older patients.12,14

In an earlier population-based study we investigated the age dependence in the circadian variation of 30,629 life-threatening cardiopulmonary emergencies (including resuscitation attempts in sudden cardiac death) observed in the Berlin emergency medical system.6 Similar to the present results, younger patients had a relatively higher event rate during the afternoon hours compared with older patients, who had a maximum between 6 AM and noon. The influence of age on the circadian pattern of sudden cardiac death suggests different external or endogenous trigger mechanisms such as differences in lifestyle or hormonal factors.

Conclusions
The age dependency of diurnal variation in ventricular fibrillation observed in the present study adds to the hypothesis of possible endogenous or exogenous factors that lead (via pathophysiological and functional modulation) to sudden cardiac death.22 It also offers clues for studying the susceptibility and conditions that ultimately trigger the catastrophic event. The results of our study underline the necessity of further investigation focusing on the circumstances of sudden cardiac death, which might be helpful in developing better strategies for prevention. Furthermore, results of electrophysiological testing and stress testing may be influenced by the time of day of the investigation23,24 and should be interpreted accordingly.

References
Circadian variation of sudden cardiac death reflects age-related variability in ventricular fibrillation.
H R Arntz, S N Willich, M Oeff, T Brüggemann, R Stern, A Heinzmann, B Matenaer and R Schröder

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