Circadian Variation of Malignant Ventricular Arrhythmias in Patients With Ischemic and Nonischemic Heart Disease After Cardioverter Defibrillator Implantation

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OBJECTIVES
The purpose of this study was to examine the circadian variation of ventricular arrhythmias detected by an implantable cardioverter defibrillator in patients with and without ischemic heart disease.

BACKGROUND
Previous studies have shown a circadian variation of ventricular arrhythmias, sudden death and myocardial infarction with a peak occurrence in the morning hours. The circadian pattern, which is similar for both arrhythmic and ischemic events, suggests that ischemia may play a critical role in the genesis of ventricular arrhythmias and sudden death. We hypothesized that, if ischemia plays an important role in the triggering of ventricular arrhythmias, the circadian pattern should be different in patients with ischemic heart disease compared with patients with nonischemic heart disease.

METHODS
The circadian variation of ventricular arrhythmias recorded by an implantable cardioverter defibrillator was studied in 310 patients during a mean follow-up of 181 ± 163 days. Two hundred four patients had a history of ischemic heart disease and 106 patients had nonischemic heart disease. The times of the episodes of ventricular arrhythmias were retrieved from the data log of each device during follow-up, and the circadian pattern was compared between the two groups.

RESULTS
During follow-up, 1,061 episodes of ventricular arrhythmias were recorded by the device in the 310 patients. Six hundred eighty-two episodes occurred in the group of patients with ischemic heart disease and 379 occurred in the nonischemic heart disease group. The circadian variation of the episodes showed a typical pattern with a morning and afternoon peak in both groups of patients with ischemic and nonischemic heart disease, but there was no significant difference between the two groups.

CONCLUSIONS
The circadian rhythm of ventricular arrhythmias in patients with ischemic heart disease is similar to patients with nonischemic heart disease, suggesting that the trigger mechanisms of the initiation of ventricular tachyarrhythmias may be similar, irrespective of the underlying heart disease. (J Am Coll Cardiol 1999;34:1560–8) © 1999 by the American College of Cardiology

A circadian variation of ischemic events, ventricular arrhythmias and sudden death is a well recognized phenomenon in patients with ischemic heart disease (1–9). Arrhythmic events show a similar circadian pattern as ischemic events, suggesting that ischemia may play a critical role in the genesis of ventricular arrhythmias and sudden death.

Most previous studies on the circadian pattern of sudden death and cardiac arrhythmias have used information from interviews of witnesses, death certificates and 24-h ambulatory electrocardiogram (ECG) recordings (1–3,10–13). Recently, more accurate information with the exact timing of these events has become available by using information from implantable cardioverter defibrillators (14–18). A circadian distribution was found in all studies and was independent of age, gender and left ventricular (LV) function. Because most of the patients in these studies had a history of ischemic heart disease, it is possible that the
circadian variation in ventricular arrhythmias and delivered therapy merely reflects a variation in ischemic events in these patients.

The aim of our study was to delineate the effect of ischemia on the triggering of ventricular arrhythmias by comparing the circadian variation in ventricular arrhythmias in a group of patients with a history of ischemic heart disease to patients with nonischemic heart disease, who all were fitted with an implantable cardioverter defibrillator owing to malignant ventricular arrhythmias, or aborted sudden death, or both. We hypothesized that, if ischemia plays an important role in the triggering of ventricular arrhythmias, the circadian pattern should be different in the two groups.

**METHODS**

**Patients.** This analysis was based on data from the clinical trial of the Medtronic (Minneapolis, Minnesota) 7219 device (19). Between March 1993 and October 1994, 820 patients were included in 66 European centers. The patients were characterized by the investigators with regard to demographic data, underlying heart disease, ejection fraction, documented arrhythmias before implant and indication for implant.

All patients were followed up at regular visits at one and three months after the implant and every six months thereafter, and as clinically indicated to evaluate suspected arrhythmic events. At each visit, complete interrogation of the device was performed, which included retrieving data for all available episodes with a printout.

**Implantable cardioverter defibrillators.** The technical characteristics of the device used (Medtronic 7219 C and D) included 0.4 to 34 J defibrillation/cardioversion shocks and antitachycardia pacing (Burst, Ramp or Ramp+). A transvenous approach was used for all new implants (n = 778). Standard surgical and electrophysiologic testing procedures were used at implant. All patients underwent a predischarge testing three to seven days after implantation during which ventricular fibrillation was induced. The device uses an automatically adjusting electrogram detection threshold, designed to avoid oversensing of signals such as T waves but to be sensitive enough to detect low amplitude signals such as in ventricular fibrillation.

The device is noncommitted, allowing therapy to be diverted if the arrhythmia terminates spontaneously. All delivered therapies were classified by the investigator as appropriate or inappropriate based on the configuration and stability of the intracardiac ECG, RR interval analysis and symptoms before or during delivered therapy. Only appropriate episodes were included in this analysis.

The device has retrievable data-logging capabilities, with information regarding the time and date for episodes fulfilling the detection criteria as well as the cycle length and response to therapy. A 5-s electrogram storage of the episode together with the corresponding marker channel are also available. The total number of episodes can be retrieved by event counters, but information regarding time and date cannot be obtained for those episodes preceding the five most recent episodes.

The time and date of the stored episodes were calculated from the time settings of the programmer. The programmers were set to the correct local time at each center at implantation and during follow-up and were adjusted for changes in daylight settings in summer and winter.

The programming of the device was left to the discretion of each investigator. The study was approved in all investigational centers by the local Ethics Committee, and all patients enrolled in the study gave their written informed consent.

**Statistics.** The circadian distribution of episodes and storms (defined as at least two episodes of ventricular arrhythmias occurring within a 10-min period but at least 1 min apart, respectively) was estimated in each individual patient. This was done by dividing the number of episodes and storms for each hour of day by the total number of this patient. The resulting individual distributions are referred to as “weighted frequencies,” because single episodes are downweighted by the reciprocal of the total number of episodes in each patient. With this weighting method, an overrepresentation of patients with frequent episodes is avoided.

The mean weighted frequencies of episodes and storms for each group of patients (ischemic/nonischemic) were superimposed by the best-fitted third-order harmonic. Third-order harmonics were chosen because lower order harmonics did not fit the data well.

We restricted our inferential analyses generally to tables with patients as sampling units, taking into account only first episodes or variables that sum up over repeated episodes. Two types of contingency tables were constructed. In both types, the two columns represent patient groups (ischemic/nonischemic) whereas the rows represent hourly intervals (type I) or 4-h intervals (type II). Four-hour intervals (beginning with the interval 0 h to 4 h) were chosen because they correspond well to third-order harmonics that divide the day into six equal-sized intervals. To compare the circadian patterns between groups for each cell of a table in a first step, a configuration frequency analysis was performed (20–23). Subsequently, a Bonferroni-Holm sequential rejection procedure (20,24) was applied for each table to keep a multiple significance level of 0.05.

Although configuration frequency analysis addresses singular differences at certain time intervals of day, log linear and logistic regression modeling address overall performance (25). Therefore, in a second step, we performed logistic regression analyses with the subgroup indicator “ischemia” as dependent variable and the 1-h or 4-h time intervals as independent categoric variables.

The advantage of the regression approach is that it can be extended easily to further variables that aggregate the
We used this advantage, and, in a third step, fitted logistic models that included as independent variables the individual percentages of episodes (storms) occurring in selected 4-h intervals.

**RESULTS**

Of the 820 patients who had an implantable cardioverter defibrillator during the study period, 310 had one or more episodes of appropriately detected ventricular arrhythmias. In these patients, a total of 3,704 episodes were recorded by the event counters. Fourteen hundred thirty-eight episodes were recorded as the last five episodes and, hence, full information, including the intracardiac ECG, marker channel, date and time of these episodes was available. The remaining 2,266 episodes, for which no such information was stored, appeared in 116 patients. In 88 patients, 50% of the episodes were recorded by event counters only.

The mean (± SD) age of the study population of the 310 patients in which ventricular arrhythmias were detected was 58 ± 13 years. Two hundred sixty-two patients were men (85%). Two hundred four patients (66%) had a history of ischemic heart disease, of whom 171 had a previous myocardial infarction. The remaining 106 patients were classified as having nonischemic heart disease: dilated cardiomyopathy (n = 59), hypertrophic cardiomyopathy (n = 7), RV dysplasia (n = 10), long QT syndrome (n = 3), valvular heart disease including mitral valve prolapse (n = 12) or primary electrical disease (n = 15).

Table 1 shows the demographic and electrophysiologic characteristics of the patients with and without ischemic heart disease. Patients with ischemic heart disease were older, more often male, had a lower ejection fraction and more often belonged to NYHA class II to III. The indication for implant and documented ventricular arrhythmias prior to implant did not differ between the two groups.

Three hundred ninety-three episodes occurred during beta-adrenergic blocking agent therapy, including sotalol. This was recorded in a total of 106 patients, 66 (32%) with ischemic heart disease and 40 (38%) without (NS).

**Table 1.** Demographic and Electrophysiologic Characteristics of Patients With and Without Ischemic Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>IHD</th>
<th>Non-IHD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SEM</td>
<td>61 ± 0.8</td>
<td>52 ± 1.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Gender</td>
<td>180/24</td>
<td>82/24</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Ejection fraction (mean ± SEM)</td>
<td>35 ± 1.1</td>
<td>46 ± 1.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (%)</td>
<td>11</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>II (%)</td>
<td>67</td>
<td>41</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>III–IV (%)</td>
<td>22</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Previous PTCA or CABG (%)</td>
<td>33</td>
<td>0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Indication for implant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmias (%)</td>
<td>65</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Aborted sudden death (%)</td>
<td>48</td>
<td>47</td>
<td>NS</td>
</tr>
<tr>
<td>Both (%)</td>
<td>17</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Documented ventricular arrhythmias before implant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia (%)</td>
<td>63</td>
<td>53</td>
<td>0.09</td>
</tr>
<tr>
<td>Ventricular fibrillation (%)</td>
<td>42</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>VT + VF (%)</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No documented ventricular arrhythmia (%)</td>
<td>9</td>
<td>15</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>No. of episodes &lt;6 mo to implant, mean (range)</td>
<td>2.8 ± 0.07</td>
<td>2.8 ± 0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with &gt;2 episodes &lt;6 mo (%)</td>
<td>62</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>Pharmacologic treatment at hospital discharge (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone (%)</td>
<td>9</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>18</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Sotalol (%)</td>
<td>17</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Class 1 antiarrhythmic agent (%)</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium-channel blocker (%)</td>
<td>4</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis (%)</td>
<td>29</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor (%)</td>
<td>48</td>
<td>52</td>
<td>NS</td>
</tr>
</tbody>
</table>

IHD = ischemic heart disease.
formed the study population. Three hundred seventy-seven episodes were recorded closer than 60 min to an initial episode and were excluded from the main analysis. Hence, 1,061 episodes were included in the main analysis for circadian variation.

Six hundred eighty-two episodes were recorded in the ischemic heart disease group and 379 in the nonischemic heart disease group. The median number of episodes in the ischemic heart disease group was 2 (range 1 to 20) and 3 (range 1 to 18) in the nonischemic heart disease group, respectively (NS). In the ischemic heart disease group, 39% of the episodes were classified as ventricular tachycardia and 61% were classified as ventricular fibrillation episodes. The corresponding figures in the nonischemic heart disease group were 40% and 60%, respectively (NS).

Figure 1 shows the mean weighted distributions of episodes, superimposed by the third-order harmonics. Both circadian patterns reveal a morning peak at about 9 to 10 AM and an afternoon peak at about 4 to 5 PM. The type I configuration frequency analysis of first episodes revealed a significant difference only in the frequencies of episodes between 6 and 7 AM (multiple p = 0.039) that was higher in patients in the nonischemic group. There were no corresponding differences in the adjacent time intervals and the type II configuration frequency analysis did not reveal any significant differences. Neither the hourly nor the four-hourly circadian pattern was a significant predictor of ischemia in a logistic regression model. Even percentages of episodes falling into any of the defined time intervals did not contribute significantly to the identification of patients with ischemic heart disease. Patients receiving antiarrhythmic or beta-blocker therapy did not show a different circadian pattern compared with patients not receiving these medications.

Arrhythmia storms. One hundred nine patients experienced arrhythmia storms, defined above. A total of 356 episodes was recorded during storms with a median number of episodes of three (range 2 to 8) for each patient. Several patients had more than one storm of episodes during the follow-up period and the total number of storms was 156. Seventy-two patients (35%) in the ischemic heart disease group and 37 patients (35%) in the nonischemic heart disease group experienced storms (NS).

Figure 2 shows the mean weighted distributions of storms, superimposed by the third-order harmonics. Figure 2B reveals a distinct bimodality in patients with ischemic heart disease, with a highly pronounced morning peak. In patients with nonischemic heart disease, a more pronounced afternoon peak was present.
The type I and the type II configuration frequency analysis of storms revealed no significant differences between patients with ischemic and nonischemic heart disease. The smallest p value (0.135) was reached for the interval between noon and 4 PM in which more storms occurred in patients with ischemic heart disease. Although the hourly circadian pattern was not significantly associated with ischemia in logistic regression, the 4-h circadian pattern just missed significance (p = 0.0795). If one includes the percentage of storms that occur between noon and 4 PM into a regression model, it is significantly associated with ischemia (p = 0.0174). According to this model, the probability that a patient who experiences all of his or her storms between noon and 4 PM is a patient with nonischemic heart disease is three times the probability of a patient who did not experience any storm in the same interval.

**DISCUSSION**

The most important finding of our study was that the circadian pattern of ventricular arrhythmias, detected by an implantable cardioverter defibrillator, was not different in patients with a history of ischemic heart disease compared with patients with nonischemic heart disease. In both groups, a typical circadian pattern was found with a morning, and less pronounced afternoon peak in the incidence of ventricular arrhythmias. These results do not support the hypothesis that, if ischemia plays an important role in the triggering of ventricular arrhythmias, the circadian pattern should be different in the two groups. The lack of difference between the groups suggests that mechanisms other than ischemia play the dominant role in the circadian variation of ventricular arrhythmias.

**Possible mechanisms underlying the circadian variation of sudden death and ventricular arrhythmias.** Several mechanisms have been proposed to contribute to the circadian rhythm found in sudden death and ventricular arrhythmias. Many of these interact, making it difficult to delineate the importance of each factor.

**Sympathetic nervous system.** The most widespread hypothesis to explain the circadian pattern of cardiac adverse events is a morning surge in sympathetic nerve activity (26–28). It has been shown that the circadian rhythm of cardiac neural regulation, using frequency domain measures of the heart rate variability, has an unfavorable profile in the morning hours (27,29–31). This could be caused by an endogenous variation in the sympathetic tonus but could also be a response to an increased activity level in the morning hours, because strenuous physical exertion has been shown to trigger ventricular arrhythmias (32). Evi-
Diurnal variation in electrophysiologic properties. Several authors have studied the circadian variation of ventricular refractoriness, either measured during an invasive electrophysiologic study (40) or noninvasively by using the telemetry function of permanent pacemakers (29,41). In all studies, there was a consistent variation with the shortest refractory periods during the waking hours and the longest during sleep. The maximal shortening of the refractory periods was observed around the hours of awakening. Kong et al. (41) found that the time of the day was the only independent predictor of ventricular refractory periods, and other factors such as catecholamine levels and serum potassium levels did not appear to influence the circadian variation. These observations are in line with the diurnal variation of maximal QT interval, in which a peak in QTc and QTc variability in the morning hours has been found, reflecting autonomic instability during this period (42).

Circadian variation of ischemic episodes. A circadian variation with a peak incidence in the morning and in the afternoon has been reported in several ischemia-related conditions such as in myocardial infarction (9,36,43), anginal attacks (44–46) and cerebrovascular stroke (47,48). There is also evidence that this is closely linked to a diurnal variation in the endothelial function (49) and biochemical markers of thrombogenicity (50–54).

Arrhythmia storms. Myocardial ischemia may create a transient substrate for ventricular arrhythmias (55). It may therefore be expected that patients with ischemic heart disease would have arrhythmia episodes (storms) more often within a short time period compared with patients without ischemia. We found, however, that the incidence of storms was similar in the two groups. It is interesting to note that the diurnal distribution of arrhythmia storms seems to be different in the two study groups (Fig. 2). Although the difference just missed statistical significance, the patients with ischemic heart disease tended to have a more pronounced morning peak and afternoon peak compared with patients with nonischemic heart disease who had a more even distribution. It can be speculated that this may be caused by ischemic episodes occurring in the morning and afternoon hours, as has been shown in previous studies on the circadian variation of ischemic events (9,36,43).

Comparison with previous studies. The early studies on circadian variation of ventricular arrhythmias and sudden death used information from death certificates, interviews with witnesses and long-term ECG recordings (1–3,10,11). Although these studies had methodologic limitations, the result was similar to later studies using information from implantable cardioverter defibrillators (14–18). The use of the storage capabilities of implantable cardioverter defibrillators represents an accurate tool for studying this issue. In all but one of the previously reported studies on circadian variation using information from implantable cardioverter defibrillators, a morning peak between 10 and 12 AM and a nadir between 2 and 5 AM were found (Table 2). Only very few patients studied had nonischemic heart disease, making it impossible to draw any firm conclusions regarding the comparison of the groups of patients.

Statistical considerations. Harmonic analysis is a popular method for analyzing circadian pattern in ventricular arrhythmias (16,17,56). However, care has to be taken so that the order of the fitted harmonic is chosen in a way that it correctly describes the modes of the pattern. One-modal harmonics will, in general, not be able to reveal the hidden structure and may impose an artifact (17). In our data, a third-order harmonic corresponding to an approximate 8-h difference of distinct modes was adequate in most of the analyses. Even after adequate choice of order, however, there remain serious limitations with regard to harmonic analysis: it is unable to cover the sharp rises and falls at the beginning and end of daily activities, it does not rule out possible additional modes of the pattern. Furthermore, the harmonic analysis assumes a periodic pattern with an even distribution. It can be speculated that this may be caused by ischemic episodes occurring in the morning and afternoon hours, as has been shown in previous studies on the circadian variation of ischemic events (9,36,43).

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negative probabilities, and the symmetric error model of at least squares fit obviously does not apply. Therefore, statistical inference based on harmonic analysis is unreliable for the circadian pattern of arrhythmias.

Some authors analyzed circadian patterns of recorded episodes as if the episodes came from different patients, resulting in high sample sizes if patients with frequent episodes were included. Such an approach would be justified only if repeated episodes in the same patient could be regarded as stochastically independent. We used our data to study this dependence structure. We found that in 56% of the cases, a morning episode was followed by a morning episode, while in 61% of the cases, an afternoon episode was followed by an afternoon episode. Moreover, in 79% of the cases, a morning storm was followed by a morning storm, while in 61% of the cases, an afternoon storm was followed by an afternoon storm. Both results differ significantly from the independence assumption and are best explained by the assumption that there exist types of patients with preferences for certain time intervals as has been suggested previously (17,56). However, stochastic inference will produce false positive results if this dependence structure is ignored. Therefore, any inferential analysis of circadian pattern should use patients and not episodes as sampling unit.

Configuration frequency analysis and logistic regression modeling can be seen as two sides of a coin. One method emphasizes rather local, the other rather global aspects. Herein, the logistic model does not confirm the rather spurious finding of a group difference at exactly 6 to 7 AM in the configuration frequency analysis of hourly frequencies of episodes. However, logistic regression can demonstrate the apparent differences in the circadian patterns of storm frequencies between patients with ischemic and nonischemic heart disease better than the configuration frequency analysis. However, only when we used the ex-post selected interval of 12 to 16 h were we able to demonstrate significant group differences in the circadian pattern of storms. Therefore, the assumption of an association between the circadian distribution of storms and ischemia remains hypothetical and requires independent validation.

One reason for our difficulty in demonstrating group differences may be that with regard to the above demonstrated dependence structure, the bimodal distributions in Figures 1 and 2 are probably best understood as mixture distributions, and ischemic and nonischemic populations may differ only in the composition of different types of patients. If this is true, only a clear identification of the type a patient belongs to will help us to demonstrate group differences due to ischemia, but this identification of types possibly will require the observation of a higher number of episodes per patient than could be observed in our population. Future trials should be designed accordingly.

**Study limitations.** The two study groups differed significantly in demographic characteristics and LV function, which may have influenced the results. Ideally, the comparison should be made with two well matched groups, but this is probably not feasible because patients with ischemic and nonischemic heart disease differ substantially, with the former disease more common at higher age and in men. In addition, it remains unclear whether the results of the study may be generalized to other patient populations. For example, patients with malignant ventricular tachyarrhythmias during the acute phase of a myocardial infarction are not included in the study because these patients are not candidates for an implantable defibrillator. Furthermore, the group of patients with nonischemic heart disease in the present study was highly heterogeneous with regard to the underlying cardiac disease. Thus, we cannot rule out that certain groups of patients may perform a different pattern of the circadian distribution of malignant arrhythmias.

In the present study, it was not possible to determine whether the patients had ischemia before the episodes of ventricular arrhythmia. Thus, in individual patients, the true role of ischemia versus other triggering factors for the initiation of ventricular tachyarrhythmias, such as an increased sympathetic activity, remains unclear. However, although the study did not show statistical differences of the diurnal distribution of arrhythmias between groups, it may be possible that myocardial ischemia plays a greater role in individuals with ischemic heart disease. As mentioned earlier, arrhythmic storms appear to show a distinct morning and afternoon peak in patients with ischemic heart disease, whereas there was a more even distribution with a slight afternoon peak in patients in the nonischemic group. Thus, a greater number of arrhythmic storm episodes in both groups are needed to prove whether the underlying heart disease, and possibly myocardial ischemia, significantly modifies the circadian variation of these arrhythmic events.

Because the memory of these devices only stores information on the time, date, type of ventricular arrhythmias, and so forth from the five last episodes, this could have influenced the results. However, a subgroup analysis, including only patients in whom only full information of all episodes was available, yielded the same results as the whole group. It is not always possible to discriminate between supraventricular and ventricular arrhythmias, even with electrograms, but previous analysis suggests that the correct diagnosis rate based on electrograms and intervals is high.

**APPENDIX**


Acknowledgment
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