Circadian Variation of Sustained Ventricular Tachycardia in Patients With Coronary Artery Disease and Implantable Cardioverter-Defibrillators

Rachel Lampert, MD; Lynda Rosenfeld, MD; William Batsford, MD; Forrester Lee, MD; Craig McPherson, MD

Background While previous studies using epidemiological data and ambulatory ECG monitoring have shown peak occurrence of sudden death and nonsustained ventricular tachycardia in the morning, none have examined circadian variation of potentially life-threatening ventricular tachycardia (VT), nor has any study observed circadian behavior of any arrhythmias in individuals followed longitudinally. We used the event memory of multiprogrammable implantable cardioverter-defibrillators to evaluate the circadian pattern of sustained VT over time.

Methods and Results Data were reviewed from 32 consecutive patients with coronary artery disease and sustained VT who had received the Ventak PRX (CPI, Inc) cardioverter-defibrillator between May 1991 and August 1993 and had experienced at least one episode of VT terminated by their device. Mean follow-up was 14±7 months. Among the 2558 episodes recorded by the device logs, VT occurrence peaked between 6 AM and noon (P=.007 by ANOVA among four 6-hour time periods). Harmonic regression revealed a morning peak at 9 AM (P<.01). This morning peak occurred in patients with both frequent and infrequent events. Among 21 patients who experienced more than four VT events, 8 (38%) had an AM peak of VT occurrence (>35% of VT between 6 AM and noon). Neither age, ejection fraction, event frequency, presenting arrhythmia, nor drug therapy distinguished patients who displayed the AM VT peak.

Conclusions In patients with coronary artery disease, sustained VT displays circadian variation with peak frequency in the morning, similar to that for sudden death. Individual patients who display specific patterns of circadian variation over time can be identified using defibrillator logs. Investigation of circadian variation of other phenomena to elucidate mechanisms of VT should focus on these patients.

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Key Words • circadian rhythm • death, sudden • defibrillation • tachycardia

Many cardiovascular phenomena display circadian variation. Epidemiological studies have demonstrated that clinical events such as sudden cardiac death,1-7 hemodynamically stable sustained ventricular tachycardia (VT),8 and myocardial infarction9-10 occur with increased frequency in the morning. Studies using ambulatory ECG (AECG) monitoring have shown in small groups of patients that ventricular ectopy11,12 and nonsustained VT13-15 vary in a similar circadian pattern. Investigators have pointed to an analogous circadian variation in physiological phenomena such as platelet aggregability, heart-rate variability, coronary blood flow, and catecholamine and cortisol levels16-20 as evidence that sudden arrhythmic death is triggered by coronary thrombosis and/or adrenergic hyperactivity that peak in the morning. However, the existing data about the circadian variation of clinical arrhythmic events have many limitations, as were summarized in a recent review.21

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While previous studies of circadian variation have been limited to either one event per person or to the 24-hour period of an AECG, the present study evaluates the pattern of sustained VT occurring in a group of patients with coronary artery disease (CAD) treated with multiprogrammable implantable cardioverter-defibrillators (ICDs) and followed longitudinally for up to 29 months. The exact recording of the event time by the device obviates the need to rely on recall of sudden-death survivors and witnesses, which has limited past studies of serious ventricular arrhythmias. This analysis shows that sustained VT demonstrates circadian variation in onset, occurring most frequently in the morning, and identifies a subset of individuals who show this pattern over time. The ability to identify diurnal variation in individuals over time may, in the future, allow identification of variables affecting this circadian pattern that may contribute to the elucidation of mechanisms of VT and sudden death and their treatment.

Methods

Patient Population
To identify patients with sustained VT and CAD, we reviewed the records of 56 consecutive patients who received a third-generation ICD (Ventak PRX, Cardiac Pacemakers, Inc) at Yale-New Haven Hospital between May 1991 and August 1993. The PRX is a multiprogrammable device that
can perform high- and low-energy cardioversion, antitachycardia pacing, and bradycardia pacing. Its event recorder stores the time of VT onset, its rate, and the therapy delivered for up to 128 events, after which more recent events replace older events in memory. All patients receiving the PRX had documented monomorphic sustained VT either spontaneously or at electrophysiological testing. Seventeen patients who had no episodes of sustained VT recorded after device implantation were excluded, as were 6 patients with underlying diseases other than CAD and 1 patient with device malfunction. The remaining 32 patients form the basis of this study.

Design
As part of their routine clinical care, patients were seen in the Arrhythmia Clinic every 2 to 3 months after ICD implantation. At each visit, the ICD log was reviewed, therapy history was printed to a floppy disk, and patients were interviewed to correlate recorded device-therapy delivery with any clinical symptoms. Device therapy was categorized as appropriate (for VT) if the event was terminated by pacing, if syncope or presyncope preceded device therapy, or if the 12 R-R intervals preceding therapy were regular and at a rate consistent with that of VT seen previously in that patient. As the Ventak PRX unit does not store event electrogams, arrhythmia episodes were categorized as atrial fibrillation if device memory demonstrated grossly irregular R-R intervals preceding device therapy or if an ECG within 24 hours of the event demonstrated atrial fibrillation with a ventricular response approaching the ICD VT recognition rate. At each visit, internal clock time was checked for accuracy and corrected for daylight-saving-time changes, and device memory was cleared.

Data for the present study were obtained by review of the clinic chart and data storage disk for each patient. Sustained VT events were defined as episodes that demonstrated mean preceding R-R intervals >250 milliseconds (rate <240 beats per minute [bpm]) and that were terminated by ICD pacing or electrical discharge. These events were tabulated for each hour of the day for each patient. Excluded from analysis were (1) rapid VT episodes with a mean preceding R-R interval <250 milliseconds (rate >240 bpm), indistinguishable from ventricular fibrillation; (2) episodes classified during clinic visits as atrial fibrillation; and (3) episodes occurring on days on which the event storage was exceeded. Each episode of VT was counted only once, irrespective of the number and type of therapies the unit delivered to terminate the arrhythmia.

Because repetitive VT events terminated by the ICD within a given hour on a single day in some patients could skew the distribution of total events, we also analyzed the distribution of "VT hours" experienced by each patient. A VT hour was defined as any hour of a given day during which one or more VT events occurred in a patient, thus excluding subsequent events in a series of repetitive VT events, to allow analysis of patterns over time without potential skewing of the data by several episodes of incessant VT. We hypothesized that if VT events followed a circadian pattern, some or all of the patients would experience VT episodes during the same hours of the day on different days.

Statistical Analysis
The significance of the distribution of VT events was assessed by grouping the events into four standard time periods: midnight (MN) to 6 AM, 6 AM to noon, noon to 6 PM, and 6 PM to MN. ANOVA was performed for significance of unequal distribution of events among the periods. To correct for unequal variances, arrhythmia frequencies were transformed to their natural log, ln(1-frequency) for the ANOVA. The significance of a possible periodic structure in the data was also tested using a single harmonic regression analysis. F tests were used to test overall significance of the harmonic regression model, and individual harmonic coefficients were tested by t test. Harmonic regression techniques were also employed as a curve-fitting technique to facilitate visual analysis of event data in the 24-hour observation interval. The equation with the highest-order harmonic containing a statistically significant sine or cosine coefficient (t test, P<.05) term was used to fit the data. The general harmonic equation is given by:

\[
\text{f}(t) = \mu + \sum_{i=1}^{p} \alpha_i \cos(\omega_i t) + \beta_i \sin(\omega_i t), \quad 0 \leq t \leq 24 \text{ hours}
\]

where \( p \) is the number of harmonics, \( \mu \) is the data mean, \( \alpha \) and \( \beta \) are the harmonic coefficients, and the angular frequency is \( \omega = 2\pi f / 24 \).

Correlation between a morning peak of VT frequency for individual patients as defined below and seven prospectively defined clinical variables (age, left ventricular ejection fraction [LVEF], total frequency of VT events, event frequency per month, presenting clinical arrhythmia, use of \( \beta \)-blockers, and use of type I or III antiarrhythmic drugs) was evaluated by Fisher's exact test.

Results

Patient Characteristics
Demographic characteristics of the 32 patients are displayed in Table 1. All patients had CAD demonstrated by coronary angiography or perfusion studies. The majority were men, with a mean age of 68 years and mean LVEF of 32%. Twenty-one patients initially presented with sustained VT, 7 with ventricular fibrillation, and 4 with nonsustained VT and syncope. During all or part of the follow-up period, 37% received \( \beta \)-blockers (including sotalol), and 46% received type I or III antiarrhythmic drugs. Mean follow-up after device implantation was 14±7 months (range, 1 to 29 months).

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics (n=32)</th>
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<tbody>
<tr>
<td>Age, y</td>
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<tr>
<td>Men, women</td>
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<tr>
<td>LVEF, %</td>
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<td>Presenting arrhythmia</td>
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<td>VT</td>
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<td>Ventricular fibrillation</td>
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<td>Nonsustained VT</td>
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<tr>
<td>Drug therapy</td>
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<td>Type I antiarrhythmics</td>
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<tr>
<td>Amiodarone</td>
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<td>Sotalol</td>
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<tr>
<td>Other ( \beta )-blockers</td>
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<tr>
<td>Events per patient</td>
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<tr>
<td>1-9 (Low frequency)</td>
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<tr>
<td>10-100 (Moderate frequency)</td>
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<tr>
<td>101-402 (High frequency)</td>
</tr>
<tr>
<td>Events per month per patient (mean, range)</td>
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</table>

LVEF indicates left ventricular ejection fraction; VT, ventricular tachycardia. Data are given as number of patients (% total) or as mean±SD. Division by frequency of events is discussed in text. Drug therapy includes treatment at any time during follow-up.
Mean analyzable time, excluding days on which device memory storage was exceeded, was 13.8±7 months (range, 1 to 26 months). ICD event memory was never exceeded during follow-up in two thirds of the patients. Of the remaining 10, only 2 had less than 80% of total follow-up available for analysis. One patient had 14.5 of 22 total months analyzable; the other had 4 out of 6 months. Based on a prospectively defined logarithmic scale of VT event frequency, 16 (50%) of the patients were categorized as displaying a low frequency (1 to 9) of VT events, 7 (22%) as a moderate frequency (10 to 100), and 9 (28%) as a high frequency (>100). The median event frequency per month was 0.92 (range, 0.14 to 40). Three patients died during the study period after 1, 6, and 20 months of follow-up, 1 of sudden death and 2 of noncardiac causes.

**Recorded Arrhythmia Characteristics**

A total of 2572 arrhythmic events were recorded in the 32 patients. After excluding 11 episodes of nonsustained VT (therapy diverted by the device) and three episodes of rapid VT and/or ventricular fibrillation, a total of 2558 events met the criteria for sustained VT and were included in the analysis.

**Circadian Variation of Ventricular Tachycardia**

In the population as a whole, VT episodes peaked between 6 AM and noon, with a secondary peak in the late afternoon, as demonstrated in Fig 1. By ANOVA, the segregation of VT episodes in the 6 AM–noon time period was significant (*P*=.007). The significance of the distribution of VT events was also tested by fitting the data to a single harmonic regression model. The fitted equation was:

$$f(t) = 106.5 + 28.1 \cos(\omega t) + 23.9 \sin(\omega t)$$

with $R^2=0.42$, *P*<.01. The peak occurred at $t=9.3$ hours, consistent with a morning peak in VT occurrence. The event data fitted to a fourth-order harmonic regression is shown in Fig 1. Statistics for the fitted curve were: $R^2=0.91$, *P*<.001 and all sine and cosine statistically significant by *t* test at *P*<.05. When the morning time period was excluded from analysis, the afternoon (noon–6 PM) showed a significant peak (*P*=.03) for the population as a whole, suggesting a secondary afternoon peak of VT events.

The distribution of VT hours also showed a morning peak of VT events (*P*=.001 by ANOVA), confirming that the morning peak of VT occurrences was a reproducible phenomenon occurring over many days of observation (Fig 2). The harmonic analysis of VT hours gave similar results with

$$f(t) = 45.6 - 9.0 \cos(\omega t) + 2.1 \sin(\omega t)$$

and $R^2=0.37$, *P*<.01, and $t=11.1$ hours the peak. The curve-fitted data shown in Fig 2 used a third-order harmonic model ($R^2=0.79$, *P*<.001).

The distribution of VT events for each patient is shown in Fig 3 (left) and for VT hours in Fig 3 (right). The predominant number of VT events occurred between 6 AM and noon in 13 (41%) of the patients. There was no predominant time period of VT occurrence in 7 patients (22%). To avoid domination of the data for the entire population by the patients with a high frequency of events, patients were also analyzed within subgroups of event frequency. ANOVA of VT event frequencies demonstrated significant segregation in the 6 AM–noon time period in patients with low total event frequencies (*P*=.04) and high event frequencies (*P*=.01), although not in the 7 patients with moderate number of total VT events.

**Circadian Variation of Individual Patients**

To examine whether circadian behavior of VT occurs as a reproducible phenomenon over time in individual patients with recurrent VT, we analyzed the 21 patients who demonstrated four or more total VT events, reasoning that these patients had the statistical chance of
FIG 3. Left, Distribution of all ventricular tachycardia (VT) events for each patient. The shaded area represents the time period during which the predominant number of events occurred for each patient. Thirteen patients had a predominance in the morning; 7 patients had no predominant time period. Bold lines segregate the population into subgroups of low, medium, and high frequency of VT events based on a logarithmic scale. Right, Distribution of VT hours for each patient. MN indicates midnight.

demonstrating at least one event in each of the four time periods into which the day was divided. We designated any time period that contained >35% of a patient's total VT events as the peak period of VT occurrence. By this definition, as shown in Fig 4, 8 (38%) of the 21 patients demonstrated a morning peak (6 AM to noon). Five patients (20%) showed peak VT frequency in the afternoon, 2 (10%) in the evening, and 2 (10%) during the night. Four patients (19%) demonstrated an even distribution of VT events over the four time periods, such that no period contained ≥35% of the total. Fig 5 demonstrates a representative circadian pattern of VT events, with a predominant morning peak and secondary afternoon peak, in a 73-year-old man in whom 107 VT events and 35 VT hours occurred over 8 months of follow-up.

Correlation of Clinical Variables With Morning Peak of Ventricular Tachycardia

The association of seven prospectively selected clinical variables with the morning peak of VT activity in the 21 patients with fewer than four VT events is shown in Table 2. By Fisher's exact test, none of these characteristics distinguished the 8 patients who demonstrated a morning peak from the 13 who did not.

Discussion

The present study is the first to document circadian variation of sustained VT in patients with CAD, as was described for sudden cardiac death by Muller et al.1 and Willich et al.10 in studies using mortality records. Previous epidemiological, clinical, and AEGG studies have suggested that ventricular arrhythmias, like many cardiovascular phenomena, occur with increased frequency in the morning. These studies have been limited, however, by imprecise timing of events because of their reliance on the recall of patients or witnesses or on estimates of timing of unwitnessed death.1,12,16 Furthermore, each patient served as only one data point in such studies, and the behavior of individual patients over time could not be evaluated. Studies using AEGG recordings have shown morning peaks in the frequency of ventricular premature depolarizations and nonsustained VT,10,13,15 but this technology still limits observations to a 24-hour period, has significant day-to-day variability, and measures only non–life-threatening arrhythmias. These shortcomings are largely overcome in the present analysis. The internal clocks of the ICD units allow precise timing of VT events. Only VT that required termination by the device, and thus was potentially life-threatening if untreated, was analyzed. This permitted us to objectively demonstrate a peak in sustained VT incidence in the morning hours between 6 AM and noon.
Statistical analysis of circadian variation of events such as VT that occur with varying frequencies in the population (ie, with skewed distribution) presents a difficulty that has been incompletely addressed in the past by excluding patients with a high frequency of events. We have shown circadian variation of VT to exist in the population as a whole by normalizing event frequencies by log transformation and by analyzing patient subgroups based on event frequency. Both high- and low-frequency groups (25 patients, 78% of the entire group) showed significant aggregation of VT events in the morning time period, suggesting that our results pertain to the population as a whole and are not an artifact resulting from inclusion of several patients with very high VT frequencies.

Analysis of VT hours also was performed to prevent domination of the data by episodes of incessant, repetitive VT occurring on a single day that might interfere with identification of patterns occurring over time. This did not alter the finding of a predominant morning peak.

When the morning time period is excluded, an afternoon peak became significant. Whether this is due to a secondary peak in the entire population, or to a subset of individuals whose primary peak occurs in the afternoon, remains to be determined in a larger population. Studies of sudden cardiac death have suggested a secondary afternoon peak in younger patients. Although our population of patients with fewer than four events contained only 3 patients under 60 years old, all showed a primary afternoon or evening peak.

Previous studies of circadian variation have analyzed trends within the entire population only. Our population displayed circadian behavior similar to the population with clinical sustained VT described by Twidale et al and to the group described in a preliminary report by D’Avila et al of patients with very rapid VT or ventricular fibrillation, also terminated by an ICD. In our study, analysis of each individual’s pattern of events over time allowed identification of patients who did and those who did not exhibit a morning peak of VT frequency. Among the 21 patients with at least four episodes of VT, 8 showed a morning peak, 9 showed other peaks, and 4 showed an even distribution. Thus, 38% of these individual patients demonstrated circadian behavior with peak VT frequency in the morning, which resulted in a statistically significant behavior in the population as a whole. Quite possibly, circadian variation of other physiological phenomena may apply to only a fraction of the population. As not all individuals display identical circadian variation, analyses of causative factors and associated variables need to be aimed at those who do.

In this study, no clinical variable was statistically associated with the likelihood of an individual displaying a morning peak of VT frequency. The small number of observations, however, makes a beta-error likely. For example, given the present proportions, a doubling of the population would show a significant morning peak of VT frequency in patients older than 60 years and in those with a presenting arrhythmia of ventricular fibrillation, whereas the other variables (LVEF, antiarrhythmic treatment, beta-blocker treatment, total frequency of VT, or event frequency per month) would remain nonpredictive. Age has been shown previously to correlate with time of arrhythmic events. In this study, as in data from the CAST trial, antiarrhythmic drug treatment did not alter circadian variation.

Correlation between circadian variation and clinical variables may help elucidate mechanisms of VT initiation. Many previous studies have shown morning peaks of both mediators of ischemia (such as platelet aggregability, coronary blood flow, and fibrinolytic activity) and clinical manifestations of ischemia, such as myocardial infarction and ST depressions on AECG. Whether the circadian variation we have demonstrated for sustained VT is due to initiation of VT by ischemia or to initiation of VT by other physiological phenomena, which also display circadian variation, is not known. Beta-Blocker treatment, which has been shown to attenuate the morning peak of ischemic events, did not change the diurnal pattern of VT in this study. While this might support a nonischemic, nonadrenergically mediated physiological trigger of the observed VT events, the small number of patients taking beta-blockers may have been insufficient to detect a meaningful effect. However, initial presentation with ventricular fibrillation, which is likely more related to ischemia, tended to correlate with morning peak of VT frequency. Whether transient ischemia plays a substantial role causing cir-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Morning Peak</th>
<th>No Morning Peak</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (≥4 events)</td>
<td>8</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>8 (100%)</td>
<td>10 (76%)*</td>
<td>18 (85%)</td>
</tr>
<tr>
<td>Presentation with VF</td>
<td>3 (37%)</td>
<td>1 (1%)*</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>LVEF ≤35%</td>
<td>7 (87%)</td>
<td>8 (62%)*</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>More than 100 events</td>
<td>4 (50%)</td>
<td>5 (38%)*</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>&gt;1 Event per month</td>
<td>6 (75%)</td>
<td>8 (62%)*</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>β-blockers†</td>
<td>4 (50%)</td>
<td>6 (46%)*</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Type I or III antiarrhythmics</td>
<td>6 (75%)</td>
<td>8 (62%)*</td>
<td>14 (67%)</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia; VF, ventricular fibrillation; LVEF, left ventricular ejection fraction; and %, percentage of patients in that column. Data are given as number of patients.

*P=NS; tincluding sotalol.

TABLE 2. Association of Clinical Variables With Morning Peak of VT Frequency in Patients With ≥4 Events
circadian variation of VT initiation in these patients remains to be answered.

Evaluation of patients with peak VT frequency at other times of the day may provide insight into other triggers of VT. Some patients with myocardial infarctions have reported triggers such as physical activity or emotional upset.26-28 One of our patients, whose peak VT frequency was in the evening, reported frequent events during episodes of heavy alcohol intake. Another, who had two of three VT events in the afternoon, reported that both occurred while gardening. These events are anecdotal, and a larger prospective investigation is needed to examine the role of other potential triggers of VT.

Limitations

We chose as a study population a homogeneous group of patients with CAD. Comparison with patients having other underlying diseases may provide further information about mechanisms of VT induction. The size of the sample precluded multivariate analysis, and more patients are needed to draw conclusions regarding the influence of clinical variables. Also, the moderate-frequency group did not demonstrate the same behavior as both the high- and low-frequency groups, which may have been due to the small number of patients in this group. No previous study has examined circadian variation of patients longitudinally, and thus there are no standard definitions of what constitutes circadian behavior in individuals. We defined a peak period of VT occurrence by criteria that seemed statistically logical: four or more total events, less than or equal to 35% of which occurred in a given time period. Our study was retrospective, which did not allow control over variables such as choice or adequacy of drug therapy. Furthermore, because of the retrospective nature of the study, we were unable to correlate peak VT frequency with wake time, which has been shown by Willich et al27 to correlate with time of sudden death. None of our patients, however, were night-shift workers, and we would expect that our data showing peak incidence of VT in the 6 AM–noon time period would also correspond to the first 3 hours after awakening in most patients. Finally, the PRX has limited event storage in memory, and some episodes of VT were not stored. There was little difference, however, in mean follow-up time available for analysis and total mean follow-up time. Also, to minimize any impact of this on data regarding circadian variation, events occurring on a day in which the PRX memory capacity was exceeded at any time during the day were excluded. Thus, all tabulated events occurred on days on which all 24 hours were available for analysis.

Conclusions

We have shown that in a population of patients with CAD, sustained VT displays circadian variation with a peak frequency in the morning, similar to that of other cardiovascular phenomena, based on timing of ICD-delivered antiarrhythmic therapy. We have also demonstrated that ICD event logs can identify those individuals who show patterns of circadian variation over time. Further research into mechanisms of circadian variation of other physiological phenomena and their correlation with VT should focus on these patients. In addition, tailoring of therapy based on circadian rhythms in the population, as has been suggested for anti-ischemic medication,9 needs to be evaluated on an individual basis.

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References

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