Circadian Variations in Ischemic Threshold and Their Relation to the Occurrence of Ischemic Episodes

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Background. The occurrence of ischemic episodes during daily activity has been reported to exhibit a bimodal circadian distribution, yet its relation to the ischemic threshold (heart rate at 1-mm ST segment depression) has not been explored.

Methods and Results. To determine whether the ischemic threshold during daily activity exhibits a circadian pattern that might relate to the frequency of occurrence of ischemic episodes, we studied the time of occurrence and the heart rate at onset of ischemia in 1,371 ischemic episodes recorded in 41 patients with stable coronary disease, positive exercise testing, and repeated ischemic episodes during ambulatory ECG monitoring (AEM). All patients had 7 days of AEM; 23 were off any anti-ischemic therapy, while 18 were on low dose of β-blockers. The occurrence of ischemic episodes exhibited the typical bimodal circadian distribution with a prominent peak between 7:00 and 11:00 AM and a second less prominent peak between 6:00 and 9:00 PM. The threshold of myocardial ischemia exhibited a different single-peaked circadian distribution; it was lowest between 1:00 and 3:00 AM and highest between 10 AM and 1 PM. Time series analyses indicated a strong hour-by-hour trend of each of the two circadian distributions, whereas the two series cross-correlated maximally at a lag of zero hours (p < 0.01), indicating a complex interplay between myocardial oxygen demand and supply in determining the occurrence of ischemic episodes during daily activity. The morning increase in the frequency of ischemic episodes could not be attributed to a reduced threshold but rather to an increase in demand. The low threshold at night-time might probably indicate that the mechanism of ischemia during these hours is reduced coronary flow due to increased coronary tone. Secondary analyses for several predefined patients’ subsets gave similar results. Patients who received low-dose β-blockers maintained the bimodal circadian distribution of the occurrence of ischemic episodes, whereas the ischemic threshold exhibited a constant pattern with no circadian changes.

Conclusions. Our results demonstrate that myocardial oxygen demand is a major determinant of daily ischemia, yet changes in the ischemic threshold that probably reflect dynamic changes in coronary tone play also an important role. The relative contribution of increased demand and decreased threshold to the genesis of ischemic episodes during daily activity can be assessed by AEM and may help to optimize medical therapy. (Circulation 1993;87:808–814)

KEY WORDS: • ambulatory ECG monitoring • silent ischemia • circadian variation • ischemic threshold

The coronary atherosclerotic plaque, regarded for many years as stable and fixed, has been shown to be capable of dilating and constricting in response to various stimuli.1,2 The coronary endothelium that in health provides a nonthrombogenic interface between the blood vessel wall and blood components displays properties that predispose to reduction in blood flow and thrombosis at the site of an atherosclerotic plaque.3,4 These changes are due to an interplay between leukocytes,5,6 platelets,3,7,8 and vascular endothelium.9–11 Atherosclerotic coronary artery segments from humans have been shown to have decreased relaxation response to acetylcholine and other endothelial-derived relaxing factor–mediated vasodilators12 and an enhanced or even paradoxical vasoconstrictive response.13–15 Such dynamic changes may result in transient myocardial ischemia16–22 or may lead to plaque rupture resulting in myocardial infarction23,24 or even to sudden cardiac death.25 All these cardiac events were shown to have a circadian distribution with a higher incidence during the morning hours, which may be related to the morning increase in platelet aggregability and decrease in fibrinolytic activity,26,27 increase in plasma catecholamine levels,28 or to an increase in coronary tone.

Several investigators have shown that ischemic episodes frequently develop in the same patient at different heart rates.29,30 Such variations in ischemic threshold are probably due to changes in coronary tone during

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Received July 10, 1991; revision accepted December 2, 1992.
daily activity. In the present study, we wanted to assess whether the threshold of myocardial ischemia (heart rate at onset of ischemia) exhibits a circadian distribution and, if so, to determine its relation to the circadian distribution of the frequency of ischemic episodes, hoping that this will help clarify the mechanism of naturally occurring ischemic episodes during daily activities.

**Methods**

Forty-one patients with stable coronary artery disease, positive treadmill stress test, and at least two ischemic episodes during 24-hour ambulatory ECG monitoring (AEM) were included in this study. There were 37 men and four women aged 42–74 years (mean, 61±9 years). The diagnosis of coronary artery disease was established according to at least one of the following criteria: angiographic evidence of significant coronary artery disease (>70% diameter narrowing in at least one major coronary artery) (n=20), documented previous myocardial infarction (n=17), and typical history of effort-induced angina with exercise-induced reversible filling defect on 201Tl scintigraphy (n=11). The 41 patients belonged to the placebo group of a multicenter trial carried out in Israel on the effect of nisoldipine on ischemia during daily activities.

All 41 patients had 7 days of AEM. The first monitoring day was the screening AEM, and within 2 weeks the patients had two periods of 3 consecutive days of AEM, 14 days apart. Before the screening AEM, all long-acting nitrates and calcium antagonists were gradually withdrawn. Twenty-three patients were monitored off anti-ischemic medications, whereas 18 were taking a constant low dose of β-blockers during the entire study period. Ten patients were treated with 25 mg atenolol per day, four patients by 50 mg atenolol per day, and four patients by propranolol 80 mg per day. No other medications except sublingual nitroglycerin were allowed during the study period.

**Ambulatory ECG Monitoring**

AEM was performed using the ACS reel-to-reel two-channel AM recorders with bipolar electrodes attached to the V3-like and V4-like positions. The Cardiodata Prodigy System combined with a PDP 11/73 computer was used for the analysis of the magnetic tapes. The ST analysis was performed in both channels in a semiautomatic-interactive method. Any deviation detected from the isoelectric PR interval was displayed on the ST trend. ECG samples were printed out in real-time, 2 minutes before onset of ST depression, at onset of ischemia (1 mm of ST depression), at maximal ST depression, at maximal heart rate, and on return to the isoelectric line. Each episode was visually verified both from the ST trend and from the real-time printouts. The ST trend enabled us to detect changes in the ST level and to correlate them to changes in heart rate at 15-second intervals. For each ischemic episode, we recorded the time of occurrence and the heart rate at onset of ischemia. An ischemic episode was defined as a transient depression of the ST segment of ≥1 mm, horizontal or downsloping, which lasted for at least 1 minute; after which, a return to baseline was observed. The end of an episode was defined as the time of return to 1-mm ST depression. The “ischemic threshold” of each episode was defined as the heart rate at which 1-mm ST segment depression was first observed.

**Statistical Analysis**

The circadian pattern of the threshold of ischemic episodes (heart rate at 1-mm ST segment depression) was evaluated by two statistical techniques—the generalized linear model and time series analysis that were applied to the raw data of all 1,371 episodes (grouped into 24-hour intervals). First, the homogeneity of the ischemic threshold was tested using a mixed unbalanced 2-way ANOVA model. In this model, the 24 1-hour periods were treated as a fixed effect, whereas the patient was treated as a random effect. Conditioned on the rejection of the homogeneity hypothesis at the 0.05 level, Tukey’s procedure for multiple comparisons (studentized range [HSD] test) was applied; this procedure controls the significance level experimentwise. The autocorrelation technique was then separately applied to the occurrence and threshold circadian distributions to determine or exclude an hour-by-hour nonrandom trend in each of these parameters. To examine a possible association between the threshold and occurrence of ischemic episodes, we finally cross-correlated these two single-cycle time series. All analyses were repeated for all predefined subsets. All circadian plots were generated using a weighted 3-hour moving average.

**Results**

The 41 patients had a total of 1,371 ischemic episodes during the 287 days of monitoring. The number of episodes per patient, per 24-hour recording, ranged from two to 13 (mean, 4.7±2.9). Ninety-one percent of the episodes were silent. The diurnal distributions of the occurrence of ischemic episodes and of their ischemic threshold are shown in Figure 1. As can be seen, there was a marked increase in the number of episodes during the morning hours between 7:00 and 11:00 AM. A second peak, even though less pronounced, was observed during the late afternoon between 5:00 and 9:00 PM. The lowest number of ischemic episodes was recorded at night (2:00 to 5:00 AM). Autocorrelation revealed a significant correlation only at a lag of 1 hour (0.841, p<0.001) and minimal absolute correlations of...
0.041, 0.069, and 0.024 at lags of 4, 10, and 18 hours, respectively, indicating a prominent hour-by-hour trend. The circadian distribution of the ischemic threshold exhibited a single peak at noon with a nocturnal dip. The lowest mean hourly ischemic threshold of 83 beats per minute was observed between 2:00 AM and 3:00 AM, followed by a slow increase toward the morning hours, reaching its highest level of 96 beats per minute at midday. Thereafter, a steady decline in the threshold during the afternoon, evening, and night was observed. The homogeneity of the ischemic threshold was tested using a two-way mixed ANOVA model. Treating the 24 1-hour periods as a fixed effect and the patient as a random effect yielded a highly significant difference ($p<0.00001$) between ischemic thresholds that were observed during different hours of the day after accounting for the within-patient variability. Multiple comparisons between hourly grouped data revealed significant differences ($p<0.05$) between the ischemic thresholds observed during the 2 hours around midnight and during the 3 hours around noon. The mean difference (95% confidence intervals) between the average ischemic threshold observed between 1:00 and 2:00 AM and that observed between midnight and 1:00 AM was 15.6 beats per minute (0.06–31.2 beats per minute). Autocorrelation revealed a significant correlation (0.658, $p<0.01$) only at a lag of 1 hour and a minimal absolute correlation of 0.034 at a lag of 5 hours, indicating a prominent hour-by-hour trend. Cross-correlation between the circadian patterns of the threshold and occurrence of ischemic episodes revealed significant correlations ($p<0.05$) with all lags that ranged between −2 and +2 hours. The two series cross-correlated maximally at a zero lag (0.684, $p<0.01$), indicating a close direct positive relation (and not reciprocal) between them. Thus, during the period of the day when the maximal frequency of ischemic episodes was observed, the threshold of myocardial ischemia was relatively high, whereas the nocturnal decrease in ischemic threshold was not associated with an increase in the occurrence of ischemic episodes.

**β-Blocker Effect**

To assess a possible effect of β-blockers on the circadian distributions of the ischemic threshold and the frequency of ischemic episodes, we analyzed the data by β-blocker use. The mean resting heart rate of the 23 patients off β-blockers was 73±13 beats per minute and that of the 18 patients on β-blockers was 66±7 beats per minute ($p=0.04$). The 23 patients without β-blockers had a total of 878 ischemic episodes (38 episodes per patient) and those with β-blockers had 493 episodes (27 episodes per patient). The occurrence and threshold of ischemic episodes in patients off β-blockers exhibited circadian distributions similar to those observed in the entire group. Mixed unbalanced ANOVA (with patient as a random effect), multiple comparisons, autocorrelation, and cross-correlation gave results similar to those obtained in the entire study group regrading the circadian distribution of the occurrence of ischemic episodes and their threshold in patients who were off β-blockers.

In contrast, in patients on β-blockers, although the occurrence of ischemic episodes maintained its typical bimodal distribution, the ischemic threshold did not exhibit any significant diurnal variations (Figure 2).

Among patients who were on β-blockers, ANOVA revealed a nonsignificant difference between ischemic thresholds that was observed during different hours of the day, whereas the occurrence of ischemic episodes differed significantly ($p<0.0001$) between different hours of the day. As expected, following the ANOVA results on the homogeneity of the ischemic threshold, the two series did not exhibit any significant cross-correlations, with correlations ranging between −0.178 and 0.215 over a range of 24 whole-hour lags.

**Mean Ischemic Threshold Effect**

We divided our patients into those who had a mean ischemic threshold ≤90 beats per minute (12 patients) and those with a mean ischemic threshold >90 beats per minute (29 patients). Those with an average ischemic threshold ≤90 had 39.7 ischemic episodes per patient compared with 30.9 among those with an ischemic threshold >90 ($p=NS$). β-Blocker use was equally distributed between the two subgroups (50% versus 41%, respectively). In both groups, the typical circadian pattern of the occurrence of ischemic episodes and their ischemic threshold was maintained (Figure 3). The same statistical techniques that were applied to the entire study group were applied to this subset analysis and gave similar results.

**Ischemic Threshold Variability Effect**

A similar analysis was performed in patients with high and low variability of their ischemic threshold (standard deviation of the heart rate at 1-mm ST depression per patient, dichotomized at <10 or ≥10 beats per minute). Due to the pronounced effect of β-blockers on the overall variability of the ischemic threshold, this subset analysis included only patients off β-blockers. There were 11 patients with a low variability (<10 beats per minute) who had a total of 427 ischemic episodes (38.8 episodes per patient) and 12 patients with a high variability (≥10 beats per minute) who had 451 ischemic episodes (37.5 episodes per patient). The circadian distributions of the occurrence of ischemic episodes and their threshold (Figure 4) displayed similar patterns and yielded similar statistical parameters to those observed in the entire study group. However, the minimal mean
hourly threshold that occurred in both subsets between midnight and 3:00 AM was lower in the high variability (72 beats per minute) than in the low variability subset (87 beats per minute), whereas the maximal mean hourly ischemic threshold was similar in the two subsets (100 versus 101 beats per minute, respectively).

Multiple comparisons between grouped data (2-hour intervals) revealed significant differences (p<0.05) between thresholds observed around noon (11:00 AM to 1:00 PM) and those observed around midnight (11:00 PM to 1:00 AM) in both subgroups. These differences, however, were more pronounced in the low-variability subgroup.

Discussion

The main findings of the present study are that the ischemic threshold during daily activities has a distinct circadian distribution, a phenomenon not reported previously, and that this pattern is not simply related to the known circadian distribution of the occurrence of ischemic episodes. The lowest ischemic threshold was observed between 2:00 and 3:00 AM; thereafter, a gradual increase in threshold was observed with the highest peak between 9:00 AM and noon, followed by a gradual decrease in the afternoon and evening. The frequency distribution of ischemic episodes exhibited two peaks, the first between 7:00 and 11:00 AM and the second, which was less pronounced, between 5:00 and 9:00 PM.

Using time series analyses further substantiated these findings; both the occurrence and threshold of ischemic episodes exhibited diurnal variation patterns that had high significant autocorrelations only at a 1-hour lag; i.e., the hour-by-hour trends seen in Figures 1–4 are statistically significant. Cross-correlation between the two time series of occurrence and threshold revealed a maximal positive crosscorrelation at a zero lag; i.e., the occurrence and threshold of ischemic episodes are positive (and not reciprocally) related to each other at any given time during the day. A possible interpretation of this finding is that the occurrence and threshold might both be modified by a common factor such as the degree of physical activity or mental arousal of the patient at any given time.

Several physiological phenomena display circadian patterns that may relate to the activity of coronary artery disease. Plasma catecholamine levels increase during the early morning hours28; an increase in platelet aggregability35 and a decrease in fibrinolytic activity.
occur during the same period. Other parameters that affect myocardial oxygen requirements such as blood pressure and heart rate also increase in the early morning hours, as do cardiac output and myocardial contractility. The clinical manifestations of coronary artery disease such as cardiac death, nonfatal myocardial infarction, and transient myocardial ischemia are also known to have a peak occurrence between 6:00 AM and noon. Several authors have suggested, therefore, that an increase in the frequency of myocardial ischemic episodes may be causally related to the greater incidence of major cardiac events during the morning hours.

In this study, we defined the ischemic threshold as the heart rate at onset of naturally occurring ischemic episodes during daily activity as recorded by AEM in active patients with documented coronary artery disease. This parameter, although not the only determinant of myocardial oxygen requirement, is undoubtedly the most important one. The other important determinant—the systolic blood pressure—is of less significance and usually fluctuates less than the heart rate. In the study of Deedwania and Nelson, an increase in heart rate of 16 beats per minute (18%) preceded the development of ischemic episodes, whereas the increase in systolic blood pressure was only 7 mm Hg (5%). During exercise testing, others have defined the ischemic threshold as the heart rate or the pressure–rate product at onset of ischemia or the time to 1-mm ST depression.

The ischemic threshold did not decrease at the time when ischemic episodes were most prevalent. This indicates, in our opinion, that the increased frequency of ischemic episodes in the morning hours is not due to reduction in ischemic threshold but rather mainly due to an increase in myocardial oxygen demand. At certain times such as 6:30 to 9:30 AM, the threshold of ischemia is not yet very high, whereas the number of episodes is already high. In our recent study, we found that a mild increase heart rate preceded 80% of the ischemic episodes. In the study of Deedwania and Nelson, an increase in pressure–rate product preceded most ischemic episodes; thus, there is convincing evidence that increased demand plays an important role in the development of ischemic episodes. Other factors such as changes in blood pressure, catecholamine levels, and platelet aggregability can also affect myocardial blood flow. The reduced nocturnal ischemic threshold found in this study suggests that coronary tone during these hours is high compared with the late morning hours. In patients with stable angina, Figueras and coworkers found that during atrial pacing, the heart rate at onset of ischemia at night was lower than during daytime. These findings are in agreement with our findings of a lower ischemic threshold during night-time.

The increase in ischemic threshold between 7:00 AM and noon during the period of maximal frequency of ischemic episodes probably indicates that during these hours the coronary arteries are dilated and, therefore, an increase in myocardial oxygen demand secondary to an increase in heart rate plays an important role in the development of these ischemic episodes. The second (afternoon) peak in the frequency of ischemic episodes occurred when the ischemic threshold was slightly reduced and, therefore, the increase in heart rate necessary to provoke an episode of ischemia was lower. During exercise the main mechanism of ischemia is an increase in myocardial oxygen demand when the coronary arteries are probably maximally vasodilated and, therefore, the threshold of ischemia is usually constant during repeated exercise tests and during different exercise testing protocols. In contrast, daily ischemic episodes occur at varying heart rates in a given patient; in those that occur at a low heart rate, marked increase in coronary tone probably prevails, whereas in those occurring at a higher heart rate, both an increase in demand and some increase in coronary tone are probably present. Several activities such as cigarette smoking, mental stress, and others have been shown to induce myocardial ischemia, probably by increasing coronary tone.

We analyzed our data according to the use of β-blockers. A decrease in ischemic threshold at night and an increase during the day were observed in the group of 23 patients off β-blockers. In the 18 patients receiving β-blockers, the ischemic threshold did not change throughout the day, whereas the characteristic pattern of an increase in the number of ischemic episodes during the morning and late afternoon hours was maintained. These patients had other evidence for the partial effect of β-blockers: their resting heart rate was lower, and the number of their ischemic episodes was also smaller (27 versus 38 episodes per patient). The reasons for the lack of diurnal changes in the ischemic threshold among patients receiving β-blockers are not clear, as in these patients the ischemic threshold of spontaneously occurring daily episodes was lower than their exercise ischemic threshold. This might provide indirect evidence that their coronary arteries maintained the capability to constrict and dilate. However, they probably were more resistant to the daily stimuli responsible for the diurnal changes in ischemic threshold. Gaglione et al found that intracoronary injection of propranolol prevented exercise-induced constriction of atherosclerotic segments. It is known that β-blockade improves endocardial-epicardial flow perfusion ratio. It is not clear whether this effect is exerted by preventing a collapse of the coronary stenosis or by direct vasodilation. It seems, therefore, that β-blockers might have a “stabilizing effect” on the coronary arteries, and this may be part of their effect in preventing ischemic episodes. The true effect of β-blockers on the circadian distribution of the ischemic threshold and the number of episodes cannot be assessed from our data, as these patients were only partially β-blocked. Furthermore, we do not have data on these patients with and without β-blockers. Previous studies have shown that in patients effectively treated with β-blockers, the number of episodes is markedly reduced, with disappearance of the morning and afternoon peaks of occurrence.

To assess whether the known two peaks of occurrence of ischemic episodes are due to two patient populations—one with more severe and one with less severe disease—we assessed the circadian distribution of the ischemic threshold and the number of episodes in patients with low (≤90 min−1) and high (>90 min−1) ischemic thresholds. In both groups, similar patterns of circadian distribution were observed.

Our data provide indirect evidence that most episodes of ischemia during daily activity are due to the...
interplay of multiple mechanisms. In some of the patients, increase in demand (heart rate) plays a more major role, whereas in others reduction in supply plays a major role. It seems that Holter monitoring can help to determine the relative contribution of each component. Such information might help to predetermine the appropriateness of anti-ischemic therapy in an individual patient.

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Circadian variations in ischemic threshold and their relation to the occurrence of ischemic episodes.
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_Circulation_. 1993;87:808-814
doi: 10.1161/01.CIR.87.3.808
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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