Morning Increase in Ambulatory Ischemia in Patients With Stable Coronary Artery Disease

Importance of Physical Activity and Increased Cardiac Demand

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Background The morning increase in asymptomatic ambulatory ischemia may be due to heightened coronary tone, increased physical activity, or both. If ambulatory ischemia is primarily due to physical activity, then alterations in the schedule of physical activity should be reflected in a corresponding alteration in the occurrence of ischemia. This study was designed to examine the relation between activity patterns and the frequency of ambulatory ischemic episodes and the effect of nadolol on these relations.

Methods and Results A double-blind, randomized, placebo-controlled, crossover trial of nadolol versus placebo was performed in 20 patients with stable coronary artery disease. At the end of each 2-week treatment phase, patients were hospitalized for 48 hours. In the hospital, there was a regular activity day (awaken and assume normal activities at 8:00 AM) and a delayed activity day (awaken at 8:00 AM, arise at 10:00 AM, and begin normal activity at noon). Ambulatory ECG monitoring was performed throughout the hospitalization. On the regular activity day, there was a morning increase in heart rate and in the number of ischemic episodes during therapy with placebo that began at 8:00 AM. In contrast, on the delayed activity day, there was a 4-hour phase shift of the increases in heart rate and the increase in ischemic episodes (ie, at noon) corresponding to the onset of physical activities. Therapy with nadolol caused a 50% reduction in the total number of ischemic episodes (129 versus 65, placebo versus nadolol; P < .02). During nadolol therapy, there was no discernible circadian peak in the number of ischemic episodes on either activity day. During placebo treatment, 87% of ischemic episodes were preceded by an increase in heart rate ≥5 beats per minute. Although nadolol caused a significant reduction in the total number of episodes preceded by a heart rate increase compared with placebo (99 versus 38 episodes, P < .04), this therapy was associated with a significant increase in the number of episodes not associated with a heart rate increase (15 versus 21 episodes, P < .002).

Conclusions The morning increase in ambulatory ischemic episodes is due to physical activity patterns. The majority of ischemic episodes are preceded by a heart rate increase, and it is these episodes that are primarily responsible for the morning increase in ischemia. Therapy with nadolol caused a reduction in the total number of ischemic episodes solely by reducing those episodes preceded by a heart rate increase. In contrast, nadolol caused a significant increase in the number of ischemic episodes not associated with a heart rate increase, perhaps in part because it potentiated coronary vasoconstriction. (Circulation. 1994;89:604-614.)

Key Words • circadian rhythm • electrocardiography • heart rate • ischemia • exercise

It is now known that the onset of acute cardiac ischemic events is not random. The frequency of myocardial infarction,1 sudden death,2 and episodes of myocardial ischemia during ambulatory activity in patients with stable coronary artery disease exhibits a marked circadian pattern, with the peak number of events occurring in the first few hours after awakening.3,5 Although reversible episodes of ischemia during routine daily activities may not be causally related to the more irreversible cardiac events such as myocardial infarction and sudden cardiac death,6 the fact that they have a similar temporal pattern of occurrence suggests that they share a common pathophysiological mechanism. The mechanism of this morning increase remains largely unknown; however, its presence has renewed interest in the investigation of the pathogenesis of acute ischemic events and the role of potential triggering activities such as physical or emotional stress.7 Recent information suggests that such factors as the sympathetic nervous system,8,9 platelet function,10 fibrinolytic activity,11 coronary vasomotor tone,12,13 and atherosclerotic plaque fissure or disruption14 may contribute to many of these cardiac events, acting alone or more likely, in concert.7 Exploration of the mechanism(s) of ambulatory ischemia may therefore not only be of value in the design of appropriate treatment strategies for patients with stable coronary artery disease; it may also provide new information concerning the causes of more life-threatening acute ischemic syndromes. Studies investigating the causes of ambulatory ischemia in patients with stable coronary
The relative roles of increased myocardial oxygen demand versus episodic coronary vasocostriction because ischemic episodes do not appear to be related to changes in platelet aggregation.5,6

The purpose of this investigation, therefore, was to determine whether the morning increase in ambulatory ischemia was due to external physical activities such as assumption of the upright posture and beginning the routine activities of daily living or whether such ischemic episodes were primarily due to a more fundamental endogenous circadian phenomenon such as changes in coronary vasomotor tone. We also sought to determine the effect of therapy with nadolol on the occurrence of ambulatory ischemia and the relation between activity levels and ischemic episodes. To investigate these questions, ambulatory electrocardiographic (AECG) monitoring was carried out in a group of patients with stable coronary artery disease. Physical activity during the morning hours was controlled in a systematic manner, and myocardial oxygen demand was assessed using minute-by-minute heart rate analysis as a surrogate.

Methods

Study Design

A double-blind, randomized, placebo-controlled trial design was used by two clinical centers. Patients were eligible for inclusion in the study if they satisfied all of the following criteria: (1) coronary artery disease documented by at least one of the following: coronary angiogram revealing one or more major coronary arteries with a ≥70% reduction in luminal diameter, previously documented myocardial infarction, or a reversible perfusion defect during stress-redistribution thallium-201 scintigraphy, (2) a stable clinical pattern of coronary artery disease with no change in frequency, severity, or ease of provocation of angina for at least 3 months before enrollment, (3) a positive exercise treadmill test defined as ≥1.0 mm of horizontal downsloping ST-segment depression, (4) four or more episodes of reversible ST-segment depression ≥1.0 mm lasting ≥1.0 minute in duration on a 48-hour screening AECG, (5) a history of myocardial infarction or cardiac surgery within 3 months before the screening visit, (2) congestive heart failure, (3) ST-segment deviation of ≥1 mm at rest or in response to hyperventilation or positional changes in the baseline AECG, (4) the presence of left ventricular hypertrophy, conduction defects, or any other condition that might interfere with the accurate interpretation of ST-segment changes, (5) atrioventricular nodal block, sick sinus syndrome, ventricular preexcitation, or the presence of an electronic pacemaker, (6) uncontrolled hypertension (diastolic blood pressure >110 mm Hg), (7) significant major systemic disease, (8) concomitant therapy with digitalis or other agents known to affect ST-segment morphology at rest or during exercise, (9) significant contraindications to β-blocker therapy, and (10) women of child-bearing potential.

Informed consent was obtained, and the patients were withdrawn from all antianginal medications except sublingual nitroglycerin as needed for relief of angina for at least 72 hours. They then underwent 48 hours of screening AECG monitoring. If this revealed four or more episodes of reversible ST-segment depression ≥1.0 mm, the patients then entered the double-blind treatment phase of the investigation (Fig 1A).

Out-of-Hospital Phase

Patients were randomized to receive initial therapy with either nadolol or placebo. The daily dose of nadolol (or placebo) was titrated from 40 mg to a maximum dose of 120 mg. The dose was increased over a 4-day period until either the maximum dose was achieved or until troublesome side effects occurred. The mean dose of nadolol was 100±24 mg daily. The maximum tolerated dose was continued to the end of each treatment phase. After completion of this titration, subjects continued the study medication for 5 to 7 days, at which time they were admitted to the hospital for a period of 48 hours.

In-Hospital Phase

During each hospital admission, the activity of study subjects was carefully controlled (Fig 1B). Patients were admitted to a private room in the late afternoon, and an AECG recorder was applied. AECG monitoring continued throughout the hospital stay. At 10:00 PM, patients retired and were left undisturbed in a darkened room until 8:00 AM the following morning. They were instructed not to rise for any reason during the night. The following morning at 8:00 AM, blood pressure and heart rate determinations were made. After these 8:00 AM measurements, activity was controlled in a different manner on each of the two hospital days. The order of each of the two activity days was randomized with each subject experiencing both activity days during each admission. The schedule of the two different activity days was as follows.

Regular Activity Day

After measurements made at 8:00 AM, patients were allowed to get up and ambulate freely. They were encouraged to perform normal morning activities including getting dressed, washing, and going for a walk. At 10:00 AM, systemic arterial pressure and heart rate were determined. At 10:30 AM, a light breakfast was served with decaffeinated coffee. At noon and 2:00 PM, repeat measurements of heart rate and blood pressure were obtained.

Delayed Activity Day

Patients remained supine after awakening in a darkened, quiet environment until 10:00 AM, at which point heart rate and blood pressure were recorded. Patients then stood for 10 minutes and subsequently remained seated quietly in a chair. A light breakfast was served with decaffeinated coffee at approximately 10:30 AM. At noon, heart rate and blood pressure measurements were repeated. Once this was completed, the subject was encouraged to ambulate freely, resuming normal activities until hemodynamic measurements and a final venipuncture were performed at 2:00 PM.

After measurements at 2:00 PM were complete, an exercise treadmill test was performed. Patients were then discharged from the clinical research center and crossed over to the alternate treatment regimen. During the first 3 days of phase 2 of the investigation, nadolol or placebo dosage was tapered off, overlapping with titration of the alternate regimen.

Ambulatory ECG Monitoring

AECG recordings were performed using Applied Cardiac Systems AM cassette recorders (Laguna Beach, Calif). Electrodes were applied to record a modified V5 and a modified aVF lead. An initial recording was made during hyperventilation and in the left and right lateral decubitus, standing, supine, and sitting positions to ensure that artifactual ST-segment deviation did not occur. If artifactual ST-segment depression was observed, the patient was excluded from the investigation. The recordings were analyzed with a CardioData Mk 4 playback system with modified software.17,18 Both the technician and the physician who reviewed the tapes were unaware of medication assignment or treatment order. An ischemic episode was defined as transient ischemic ST-segment depression ≥1.0 mm lasting ≥1 minute. The onset of each episode was defined as the time at which the ST segment became depressed by ≥0.5 mm, and the offset was defined as the time after the peak depression ≥1.0 mm at which the ST...
segment returned toward baseline and became depressed <0.5 mm. After an episode of ST-segment depression, the baseline had to remain stable for ≥5 minutes before new ST-segment depression could qualify as a discrete additional episode. The variables evaluated included (1) the number of episodes of ischemic ST-segment depression, (2) the average duration of ischemia in minutes during each episode, and (3) the total duration of ischemia per 24 hours. Other variables analyzed included (1) the maximum ST-segment depression during the episode and (2) the product of the maximum depth of ST-segment depression and the duration of the episodes (the ST product).

Heart rate analysis also was performed to compare ischemic episodes preceded by an increase in heart rate with ischemic episodes not preceded by an increase in heart rate. Minute-by-minute heart rate patterns during the 20-minute period before individual episodes were examined. A 3-minute moving average was calculated such that each heart rate value represented the mean of itself, the heart rate during the preceding minute, and the heart rate during the subsequent minute. Episodes were then classified on the basis of whether or not a ≥5 beats per minute increase in heart rate occurred during the period from 1 to 20 minutes before episodes. Those episodes that were preceded by a ≥5 beats per minute increase in heart rate during this time period were termed “heart rate–associated episodes”; those that were not preceded by a ≥5 beats per minute increase during this time period were termed “non–heart rate–associated episodes.” This was done to determine whether there was a difference in the temporal occurrence or in the response to therapy of ischemic episodes preceded by an increase in heart rate (ischemia that may be due, at least in part, to a primary decrease in myocardial blood supply). A further analysis was performed to determine the absolute frequency of occurrence of these ≥5 beats per minute increases in heart rate throughout the day, and the total for each 2-hour time bin during the 24-hour day was recorded. This analysis allows for a comparison of the temporal distribution of heart rate increases associated with an ischemic episode and those heart rate increases not associated with an ischemic episode.

Exercise Treadmill Testing

Exercise treadmill tests were performed using the standard Bruce protocol. Twelve-lead ECGs were recorded at the end of each minute of exercise and recovery until the ST-segment morphology returned to baseline. Identification of the heart rate when the ST segment first reached −1.0 mm depression was noted.

Statistical Analysis

The temporal distribution of ischemic episodes occurring in 2-hour bins was examined by means of a polynomial regression analysis to determine the time at which the peak in ischemic episodes occurred. To determine if there was a difference in the number or characteristics of ischemic episodes at different times of the day, the frequency distribution of ischemic episodes was examined by means of a χ² analysis with the 24-hour day divided into three 8-hour time periods. Eight-hour time bins were used in this analysis to provide a sufficient number of episodes of different heart rate patterns in each bin to allow for meaningful statistical comparison.
Hypothesis tests to determine the impact of factors such as treatment and activity on continuous variables (blood pressure, heart rate, the total number of episodes of ambulatory ischemia, and other characteristics of ischemic episodes) were analyzed using ANOVA with linear contrasts for comparisons of specific cell means. The number of ischemic episodes was grouped and classified to determine whether there was a significant association with treatment, activity schedules, and time of day. A χ² test of independence was used to test the association between these factors (eg, levels of treatment [placebo versus nadolol] and time of day). Paired and unpaired t tests (two-tailed) were used to determine changes from baseline and simple two-group mean comparisons. Simple linear regression was used to correlate heart rate at onset of ≥1.0 mm of ST-segment depression during the exercise test as compared with that seen during episodes of ischemia on AECG monitoring. The correlation between the two heart rate thresholds seen during placebo therapy was compared with that seen during nadolol therapy by performing an unpaired t test on the residuals determined from the regression. Exact P values are reported for values <.05. All data are expressed as mean±SEM unless indicated otherwise.

Results

Patient Population

From a group of 40 screened patients from two institutions, a total of 20 entered the randomized protocol. There were 19 men and 1 woman; their average age was 61±9 years. Of these 20, 1 patient developed unstable angina after completing the first treatment arm (which was nadolol), and thus his results are not available for analysis of comparative efficacy. The remaining 19 patients successfully completed all phases of the investigation.

Effect of Nadolol on Heart Rate and Blood Pressure

Compared with placebo, nadolol decreased mean systolic blood pressure during the in-hospital phases of the investigation from 128±3 to 118±4 mm Hg (P<.05), mean diastolic blood pressure from 78±2 to 71±2 mm Hg (P<.02), and mean heart rate from 74±3 to 55±1 beats per minute (P<.001).

Effect of Nadolol on Ischemic Episodes

There were 194 episodes of ischemia during a total of 1872 hours of AECG recordings, of which 130 (61%) were asymptomatic. Nadolol was associated with a significant reduction of most manifestations of ischemia during ambulatory monitoring when compared with placebo (Table 1). In comparison with placebo, nadolol resulted in a 50% reduction in the total number of episodes (P<.02), a 50% reduction in the mean duration of individual episodes (P<.002), a 314% reduction in the total duration of ST-segment depression per 24 hours (P<.02), and a 53% reduction in the mean ST product per episode (P<.003). Nadolol therapy was not associated with a significant reduction in the mean maximum ST-segment depression per episode.

Effect of Activity Patterns on the Temporal Distribution of Ischemic Episodes

During placebo treatment, there were no differences in the total number of ischemic episodes nor in the cumulative daily duration of ischemia on the regular versus the delayed activity day (Table 2). However, there was a dramatic shift in the temporal occurrence of the episodes based on the timing of physical activity: On the regular activity day, the typical circadian variation of episodes was observed, manifested by an increase in the number of episodes that was greatest between 8:00 AM and noon (Fig 2). By contrast, on the delayed activity day, the onset and peak occurrence of ischemic episodes were shifted to a time 3 to 4 hours later, coinciding with the onset of physical activity (peak incidence between noon and 4:00 PM; Fig 2). There was a significant interaction between the two different activity days and the temporal distribution of ambulatory ischemic episodes for patients on placebo (χ²=13.2, P=.004). The polynomial regression analysis revealed that the best fit to the frequency distribution of episodes was obtained by means of a fifth-order polynomial, with the peak number of episodes occurring at approximately noon during the regular activity day, whereas on the delayed activity day, this peak was delayed until 3:00 PM (Fig 2).

During therapy with nadolol, there was similarly no difference on the two activity days in the total number of ambulatory ischemic episodes (P=NS) or in the total duration of ischemia (P=NS) (Table 2). Therapy with nadolol abolished the peak in ambulatory ischemic episodes associated with the morning onset of physical activities on the regular activity day (Fig 3). On the regular activity day (Fig 3A), nadolol was more effective in preventing episodes in the morning and early afternoon than it was during the evening and

### Table 1. Effects of Nadolol Therapy on Episodes of Ambulatory Ischemia

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Nadolol</th>
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<tbody>
<tr>
<td>Total No. of episodes</td>
<td>129</td>
<td>65*</td>
</tr>
<tr>
<td>Mean duration of episodes, min</td>
<td>16.0±2.0</td>
<td>8.0±1.5†</td>
</tr>
<tr>
<td>Total duration of ischemia per 24 hrs (min)</td>
<td>35.9±4.5</td>
<td>11.4±2.1*</td>
</tr>
<tr>
<td>Mean ST product per episode, mm · min</td>
<td>-26.5±3.7</td>
<td>-12.5±2.8†</td>
</tr>
<tr>
<td>Mean maximum ST depression per episode, mm</td>
<td>-1.4±0.1</td>
<td>-1.4±0.1</td>
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*P<.02 vs placebo; †P<.003 vs placebo.

### Table 2. Effect of Activity Patterns on Episodes of Ambulatory Ischemia

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<th>Placebo</th>
<th>Nadolol</th>
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<tr>
<td>Total No. of episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular activity day</td>
<td>57</td>
<td>36*</td>
</tr>
<tr>
<td>Delayed activity day</td>
<td>63</td>
<td>29*</td>
</tr>
<tr>
<td>Duration of episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular activity day, min</td>
<td>13.2±2.2</td>
<td>9.6±2.5*</td>
</tr>
<tr>
<td>Delayed activity day, min</td>
<td>12.3±1.8</td>
<td>6.1±1.4*</td>
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*P<.05, nadolol vs placebo.
nighttime hours (Table 3). Nadolol was associated with a 68% reduction in ischemic episodes occurring in the time period from 8:00 AM to 4:00 PM (P=.03). During the remainder of the 24-hour period, however, from 4:00 PM to 8:00 AM, nadolol had no significant effect on the number of episodes (23 versus 26 episodes, P=NS).

Relation Between Heart Rate Patterns and Ischemic Episodes

The mean heart rate 5 minutes before and at the onset of ischemic ST-segment depression during AECG monitoring was lower on nadolol than on placebo therapy (57±2 and 67±3 beats per minute versus 88±2 beats per minute).
and 104±2 beats per minute, respectively, on placebo; each *P<.001). Although the maximal heart rate during each episode was also significantly lower during nadolol therapy than during placebo (91±2 versus 127±3 beats per minute, *P<.001), the increase in heart rate from 5 minutes before episodes to the peak heart rate during episodes was similar for both treatment groups (34 beats per minute on nadolol versus 37 beats per minute on placebo, *P=NS).

Examination of minute-by-minute heart rate means before episodes reveals that the heart rate pattern on placebo was stable until 3.0±0.7 minutes before the beginning of an ischemic episode, at which time it rose by 6 beats per minute before the onset of ischemia (Fig 4). The heart rate pattern before ischemic episodes during nadolol therapy was similar; the mean heart rate was stable until 5.0±0.5 minutes and rose by 6 beats per minute before the onset of ST-segment depression (Fig 4).

### Relation Between Heart Rate Patterns and Ischemic Episodes Occurring at Different Times of the Day

On placebo, the heart rate increase before ischemic episodes was similar during the morning and early afternoon (8:00 AM to 4:00 PM) compared with the rest of the day (Fig 5). By contrast, however, during therapy with nadolol there was a significantly smaller increase in the mean heart rate increase preceding ischemic episodes occurring in the late afternoon and night compared with episodes occurring during the remainder of the day (6±2 versus 13±4 beats per minute, *P<.001).

**Table 3. Effect of Time of Day and Type of Therapy on Episodes of Ambulatory Ischemia**

<table>
<thead>
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<th>Placebo</th>
<th>Nadolol</th>
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<tbody>
<tr>
<td><strong>Total No. of episodes: regular activity day</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00 AM to 4:00 PM</td>
<td>41</td>
<td>13*</td>
</tr>
<tr>
<td>4:00 PM to 8:00 AM</td>
<td>26</td>
<td>23</td>
</tr>
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</table>

*P=.03, nadolol vs placebo.

Characterization of Ischemic Episodes Based on the Presence or Absence of Heart Rate Increase Preceding the Onset of Ischemia

During placebo treatment, 87% of ischemic episodes were associated with a heart rate increase, whereas 13% were non–heart rate associated (Table 4). In contrast, during nadolol therapy, 64% of the episodes were heart rate associated, whereas 36% were non–heart rate associated (heart rate associated versus non–heart rate associated, nadolol versus placebo; *P<.002, χ²). Thus, nadolol caused a significant reduction in the total number of ischemic episodes by exclusively reducing heart rate–associated or presumably demand-mediated episodes, whereas it was associated with a significant increase in the number of non–heart rate–associated or presumably supply-mediated episodes.

**Effect of Medication and Structured Physical Activity on Circadian Variation of Heart Rate–Associated and Non–Heart Rate–Associated Episodes of Ischemia**

During therapy with placebo on the regular activity day, heart rate–associated episodes displayed a circadian variation similar to that seen when all episodes were combined, with a peak incidence in ischemia between 8:00 AM and noon. On the delayed activity day, the peak incidence in heart rate–associated episodes was shifted 4 hours later. Of note, there was no clear circadian variability in the frequency distribution of non–heart rate–associated ischemic episodes on either activity day.

During nadolol therapy, there was no circadian variability in the frequency of either type of episode. Because nadolol appeared to be more effective in preventing morning and early afternoon ischemic episodes, the effect of time of day on the relative distribution of episode type was investigated during the regular activity day. For patients on placebo, 94% of episodes between 8:00 AM and 4:00 PM were heart rate associated, whereas only 6% were non–heart rate associated (Table 4). A similar distribution of episode type was found during the remainder of the day (88% heart rate–associated episodes and 12% non–heart rate–associated

![Fig 4](http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.107.183235/-/DC1/DC1.png)
episodes, \( P=\text{NS} \)). In contrast, during therapy with nadolol, there was a different distribution of episode type based on heart rate activity: 77% of episodes were heart rate associated and 23% were non–heart rate associated from 8:00 AM to 4:00 PM, but from 4:00 PM to 8:00 AM, only 53% of episodes were heart rate associated and 47% were non–heart rate associated (Table 4, \( P<.03 \)).

Thus, during therapy with nadolol, there was a significant increase in both the absolute number and proportion of non–heart rate–associated episodes occurring from 4:00 PM until 8:00 AM.

The analysis of the occurrence of heart rate increases \( \geq 5 \) beats per minute throughout the day is presented in Fig 6, and the results are displayed superimposed on the frequency distribution of ischemic episodes on each type of day and on each form of therapy. This figure demonstrates that the frequency distribution of ischemic episodes closely parallels the frequency of occurrences of increases in heart rate. On placebo, the morning increase in the occurrence of increases in heart rate is shifted 4 hours in an analogous manner to the shift that occurred with episodes of ambulatory ischemia (Fig 6A). For patients on nadolol, although there is a much lower frequency of heart rate increases during waking hours, the increases in heart rate observed are shifted 4 hours from the regular to the delayed activity days. Despite this low frequency of heart rate increases on nadolol, episodes of ischemia are nevertheless observed, particularly during the afternoon and evening time periods.

Examination of the mean hourly heart rate values for patients on placebo (Fig 7A) reveals a morning increase in mean heart rate on the regular activity day that occurs 4 hours later on the delayed activity day. Interestingly, during nadolol therapy (Fig 7B), there is very little change in mean hourly heart rate on either activity day.

### Relation Between Heart Rate at the Onset of Ischemia During Exercise Testing Compared With That Seen at the Onset of Ischemia During AECG Monitoring

The heart rate at the onset of 1.0-mm ST-segment depression was consistently higher during exercise testing compared with that during AECG monitoring during both placebo and nadolol therapy (mean difference, 19\( \pm \)3 beats per minute during placebo and 22\( \pm \)4 beats per minute during nadolol; \( P=.0001 \) for each). There was a significant correlation between heart rate at the onset of \( \geq 1.0 \)-mm ST-segment depression during exercise testing when compared with that found at the onset of \( \geq 1.0 \)-mm ST-segment depression during AECG monitoring. During nadolol therapy, the correlation between the two heart rate ischemic thresholds was high (\( r=.67, P=.004 \)), whereas during placebo therapy, it was somewhat less (\( r=.45, P=.0004 \)). There was no significant difference between the two correlation coefficients, but the sample size was very small.

### Discussion

This investigation demonstrates that the morning increase in the frequency of episodes of ambulatory

### Table 4. Characterization of Episodes Based on Preceding Heart Rate Activity

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<tr>
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<th>Placebo</th>
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<tr>
<td>Total No. of episodes</td>
<td></td>
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<tr>
<td>Heart rate–associated episodes (%)</td>
<td>99 (87)</td>
<td>38 (64)*</td>
</tr>
<tr>
<td>Non–heart rate–associated episodes (%)</td>
<td>15 (13)</td>
<td>21 (36)†</td>
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<tr>
<td>Total No. of episodes during regular activity day</td>
<td></td>
<td></td>
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<tr>
<td>8:00 AM to 4:00 PM</td>
<td></td>
<td></td>
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<tr>
<td>Heart rate–associated episodes (%)</td>
<td>34 (94)</td>
<td>10 (77)*</td>
</tr>
<tr>
<td>Non–heart rate–associated episodes (%)</td>
<td>2 (6)</td>
<td>3 (23)</td>
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<tr>
<td>4:00 PM to 8:00 AM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate–associated episodes (%)</td>
<td>14 (88)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Non–heart rate–associated episodes (%)</td>
<td>2 (12)</td>
<td>8 (47)‡</td>
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*\( P<.04 \) \( \chi^2 \), nadolol vs placebo.
†\( P<.002 \) \( \chi^2 \), heart rate vs non–heart rate associated, nadolol vs placebo.
‡\( P<.03 \) \( \chi^2 \), heart rate vs non–heart rate associated, nadolol vs placebo.
myocardial ischemia in patients with stable coronary disease is strongly dependent on activity patterns associated with the morning hours after awakening. During placebo therapy, patients involved in the regular activity day manifested a morning peak in ischemic episodes that is similar to that seen in other investigations.3-5 By contrast, during the delayed activity day, this temporal distribution of ischemic episodes was shifted coincident with the delayed onset of daily activities. The fact that the morning increase in ambulatory ischemia was closely tied to initiation of daily physical activities is consistent with previous reports that the morning increase in ambulatory ischemia and acute myocardial infarction is dependent on the time of awakening rather than being an intrinsic circadian phenomenon.3,19 A unique feature of the current investigation is that previous studies adjusted the onset of cardiac events for waking time only; this is the first study to dissociate waking time from activity time.

Nearly all ischemic episodes occurring in the morning and early afternoon are associated with increases in heart rate and, presumably, are related to increases in myocardial oxygen demand. Consequently, β-adrenergic receptor blockade with nadolol was extremely effective in preventing the morning increase in ambulatory ischemia. By contrast, nadolol therapy was actually associated with an increase in the number of ischemic episodes not associated with an increase in heart rate. This increase in presumably supply-mediated episodes, which may be due in part to episodic coronary vasoconstriction, occurred primarily in the late afternoon and nighttime, suggesting that nadolol therapy may have had deleterious effects on myocardial oxygen supply during that period.

Pathogenesis of Ambulatory Ischemia and Its Relation to the Morning Increase in Ischemic Episodes

Analysis of patterns of heart rate change before episodes of ischemia can provide important information concerning the nature of ischemic episodes and their response to treatment. At present, there is conflicting information regarding whether ambulatory ischemic episodes are precipitated by increases in myocardial oxygen demand or decreases in myocardial oxygen supply.20-24 Discordant observations have been reported because there has been no agreement as to the criteria that should be used to gauge an increase in heart rate before ischemic episodes. Recent data from our laboratory suggest that there are at least two separate populations of ambulatory ischemic episodes distinguished by the presence or absence of an increase in heart rate ≥5 beats per minute during the 30-minute period preceding the onset of ST-segment depression.25 Analysis of the heart rate patterns in the present study...
confirms these prior observations. In this investigation, the majority of ischemic episodes were associated with an increase in heart rate ≥5 beats per minute during the 20-minute period before episodes, whereas in a smaller number of episodes, no such heart rate increase was seen. Although analysis of heart rate data alone does not provide a complete assessment of changing myocardial oxygen demands, heart rate patterns are a reasonable and practical surrogate to gauge changes in oxygen demands because Deedwania and Nelson23 have demonstrated that increases in heart rate are almost invariably associated with a concomitant increase in systolic blood pressure, the second principal determinant of myocardial oxygen demand. It must be emphasized, however, that the sympathetic activation responsible for an increase in heart rate and blood pressure may also lead to episodic coronary vasoconstriction.26,27 Thus, an increase in heart rate may serve primarily as a marker for sympathetic activation, and the resultant ischemia that may occur may be due to a complex interaction of increased myocardial oxygen demand and decreased oxygen supply. Regardless of the relative contributions of increase in oxygen demand versus decrease in oxygen supply, sympathetic activity remains an important determinant of the development of myocardial ischemia, and heart rate activity is a useful surrogate to reflect that activity.

We observed in this study, as have others,28 that the heart rate at the onset of ischemia during exercise testing was consistently and significantly higher than the heart rate at the onset of ischemia during AECG monitoring. This observation suggests that there may be heightened coronary vasoconstriction during routine daily physical and emotional activities such that ischemia is provoked at a lower heart rate in a normal ambulatory usual environment compared with the artificial laboratory environment used for exercise testing.

Although coronary vasoconstriction may contribute to the pathogenesis of ambulatory ischemia, it is evident from our study that the majority of episodes also require an increase in heart rate. Our results show clearly that a 4-hour delay imposed on the onset of physical activities leads to an identical 4-hour delay in the increase of the mean hourly heart rate, the frequency of increases of heart rate ≥5 beats per minute, and the occurrence of myocardial ischemia (Figs 6 and 7). The fact that many increases in heart rate do not lead to the development of an ischemic episode most likely reflects the fact that an increase ≥5 beats per minute alone is insufficient to provoke ischemia. Andrews et al25 re-
ently demonstrated that the likelihood of developing ischemia associated with an increase in heart rate ranges from 4% to 60%, based on an interaction of a number of important heart rate variables: the magnitude of heart rate increase, the duration of heart rate increase, and the baseline heart rate from which the increase in heart rate began. In this study, the only heart rate variable we identified was an increase ≥5 beats per minute, and we did not investigate the other heart rate variables.

Previous investigators have suggested that the morning increase in ambulatory ischemia may reflect a lowered ischemic threshold caused by a morning increase in coronary artery tone, similar to the observations in animal investigations and in patients with Prinzmetal’s variant angina. However, these reports may not be representative of what occurs in a population with stable coronary artery disease. Quyyumi and colleagues reported that the ischemic threshold during exercise testing in stable coronary patients was lower at 8:00 AM and 9:00 PM compared with noon and 5:00 PM, presumably because of heightened coronary tone in the morning and at night. However, Benhorin and colleagues observed during ambulatory ECG monitoring that the heart rate threshold for ischemia was actually higher in the morning than in the evening, suggesting that coronary tone may actually be higher at night. Our results indicate that the heart rate increase preceding ischemia was similar throughout the day on placebo treatment but that during nadolol therapy, the increase in heart rate before ischemia was lower in the late afternoon and night than at other times of the day, a phenomenon perhaps reflecting an exacerbation of coronary tone by the β-adrenergic blocker later in the day. There appears to be agreement that coronary tone may be heightened later in the day. The differences concerning whether coronary tone is also increased in the morning may be due to small sample sizes used in each study or to different testing methodologies: The reduced ischemic threshold in the morning has only been observed from supervised exercise testing and not from ambulatory ECG monitoring while the patient is exposed to the routine physical and emotional stresses of daily life.

Our observations concerning the distribution of heart rate–associated and non–heart rate–associated episodes at different times of the day also provide some insight into the pathogenesis of ambulatory ischemia and its response to therapy. On the regular activity day during therapy with placebo, the vast majority of episodes (approximately 90%) were preceded by an increase in heart rate ≥5 beats per minute at all times during the day. During nadolol therapy, there was a significant reduction in the number of heart rate–associated episodes on both activity days, but there was also a significant increase in the absolute number and relative proportion of non–heart rate–associated episodes. These results suggest that β-adrenergic receptor blockade is effective in preventing ischemic episodes precipitated by an increase in heart rate but that it is less effective and may even aggravate those episodes not associated with an increase in heart rate that may be due in part to episodic coronary vasoconstriction. These observations extend the observations by Andrews et al that propranolol markedly reduced ischemic episodes associated with a preceding heart rate increase but was much less effective in reducing episodes not preceded by a heart rate increase.

**Clinical Implications**

This investigation demonstrates that the morning increase in ambulatory ischemia is closely related to the morning increase in physical activity and not to an endogenous phenomenon occurring at that time of the day. In susceptible individuals, this morning increase in cardiac demand could act as a trigger for irreversible cardiac events. Nadolol only reduced the frequency of ischemic episodes occurring in the morning and early afternoon and only those episodes associated with an increase in heart rate. Consistent with these findings is the observation by others that use of β-adrenergic blockers is associated primarily with a reduction in myocardial infarction and sudden death occurring during the morning hours. This study also indicates that β-adrenergic blockade increases the number of ischemic episodes not preceded by an increase in heart rate and that these episodes are more frequent in the evening and at night. These events may be due in part to episodic coronary vasoconstriction and may be related to the secondary evening peak in the incidence of myocardial infarction and sudden death that have been observed frequently, particularly among patients on a β-blocker. Finally, our data suggest that combination therapy of a β-adrenergic blocking agent with either an organic nitrate or a calcium channel antagonist may be particularly valuable because both of these latter agents have been reported to be effective in the management of ischemic episodes not mediated by increases in heart rate.

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