Subsets of Ambulatory Myocardial Ischemia Based on Heart Rate Activity
Circadian Distribution and Response to Anti-Ischemic Medication

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Background. Identification of whether episodes of ambulatory ischemia are caused by increases in myocardial oxygen demand or to episodic coronary vasoconstriction in patients with stable coronary disease may be important to guide selection of optimal anti-ischemic therapy and to gain insight into mechanisms responsible for adverse cardiac events.

Methods and Results. Mean minute heart rate activity during ambulatory ECG (AECG) monitoring was determined for 50 patients treated with propranolol, diltiazem, nifedipine, or placebo in a randomized, double-blind, crossover trial. Periods of heart rate increases of various magnitudes and durations and starting at various baseline heart rates on each therapy were identified throughout each 48-hour AECG recording, and the proportion of these periods associated with an ischemic episode was determined. The circadian variation of ischemic episodes categorized by the presence or absence of an increase in heart rate was analyzed. Eighty-one percent of ischemic episodes were preceded by an increase in heart rate >5 beats per minute. The likelihood of developing ischemia associated with a heart rate increase was proportional to the magnitude and duration of the heart rate increase and the baseline heart rate before the increases in heart rate: likelihood ranged from 4% when the heart rate increased 5-9 beats per minute and lasted <10 minutes to 60% when the heart rate increased >20 beats per minute and lasted >40 minutes. The likelihoods of developing ischemia based on changes in the heart rate variables were similar for each of the therapies. Propranolol therapy significantly reduced the magnitude and duration of heart rate increase and the baseline heart rate compared with therapy with placebo, diltiazem, or nifedipine (P<.001). Ischemic episodes associated with a heart rate increase displayed a daytime peak, whereas ischemia occurring without a heart rate increase occurred evenly throughout the day. Propranolol reduced the proportion of heart rate–related ischemic episodes and increased the proportion of non–heart rate–related episodes compared with placebo (P<.02), and nifedipine exerted the opposite effect (P=.005). Multivariate analysis indicated that the probability of developing ischemia was strongly associated with heart rate variables and was unaffected by time of day.

Conclusions. Most episodes of ambulatory ischemia are associated with a preceding period of increased heart rate. The likelihood of developing ischemia is predicted by heart rate variables and unaffected by time of day. Anti-ischemic efficacy is generally a result of the medication’s efficacy in reducing heart rate variables. A minority of ischemic episodes are not associated with preceding periods of increased heart rate, may be caused by episodic coronary vasoconstriction, and are more effectively reduced by nifedipine than propranolol. (Circulation 1993;88:92-100)

Key Words • ambulatory ECG • ischemia • propranolol • nifedipine • diltiazem

In the past decade it has become appreciated that most episodes of ischemia occurring in the ambulatory setting are clinically asymptomatic and may be caused in part by pathophysiological mechanisms different from those responsible for ischemia provoked during a supervised exercise test.1–3 Ischemia occurring during a multistage exercise test is caused primarily by a progressive increase in myocardial oxygen demand, whereas it has been suggested that the physical and emotional stresses of daily life may lead to ambulatory episodes of ischemia caused in part by episodic coro-
nary vasoconstriction.4-8 Using heart rate patterns preceding episodes of ischemia as a surrogate for myocardial oxygen demand, some investigators have observed that the majority of episodes are preceded by an increase in oxygen demand,9-11 whereas other investigators observe that most episodes occur in the absence of an increase in demand and presumably are caused by episodic coronary vasoconstriction.1,2,12 However, uniformity is lacking in the criteria used to gauge an increase in heart rate before an episode.

Identification of the mechanism responsible for ambulatory ischemia may be important because, if most episodes are related to an increase in heart rate, β-adrenergic blockers should be optimal therapeutic agents, whereas if episodes are not associated with an increase in heart rate, calcium channel antagonists may be more effective therapy. If different pathophysiological mechanisms lead to episodes of ischemia during daily life, the relative importance of each of these mechanisms may change throughout the day.

The Angina and Silent Ischemia Study (ASIS)13 was designed primarily to evaluate the effects of single-agent drug therapy on episodes of ambulatory ischemia and found that only propranolol was associated with a marked reduction in the frequency and duration of daily ambulatory ischemia, that diltiazem was associated with a significant but much less marked reduction in the frequency of episodes, and that nifedipine had no significant effect on any measured variable of ambulatory ischemia. The medications used in ASIS were selected because of their very different effects on heart rate, and the data base provides a unique opportunity for a detailed analysis of the heart rate patterns occurring throughout the day and in association with ischemic episodes. Analysis of the heart rate patterns observed in the placebo arm of the study provides insight into the “natural” heart rate patterns preceding episodes of ischemia, and analysis of heart rate patterns occurring on propranolol, diltiazem, and nifedipine provides insight into possible differential effects of these medications. We speculated that episodes of ischemia could be categorized into distinct types corresponding to those associated with a heart rate increase and those not associated with a heart rate increase and that these different types of episodes may follow different circadian patterns and respond differently to medications.

Methods

Study Design

Ambulatory ECG (AECG) recordings from the ASIS were used for all analyses. ASIS was a randomized, double-blind, multicenter, crossover trial comparing the single-agent anti-ischemia efficacy of propranolol, diltiazem, nifedipine, and placebo. The protocol has been described in detail.13 In brief, patients were eligible for study participation if they had documented evidence of coronary artery disease, had a stable pattern of angina pectoris, exhibited a positive exercise treadmill test characterized by both horizontal ST segment depression ≥1.0 mm and typical angina pectoris, and demonstrated six or more episodes of reversible ST segment depression ≥1.0 mm during 48-hour AECG monitoring. Eligible patients were randomized initially to one of the four treatments, and the dose was titrated over the course of 1 week to the maximally tolerated dose (propranolol-LA, mean daily dose 292 mg/day; diltiazem-SR, 350 mg/day; nifedipine, 79 mg/day). The patients continued on the therapy for a second week, at the end of which time an exercise test and 48-hour AECG were performed. Patients were then randomly crossed over to each of the other treatments in a serial manner. At the end of each 2-week treatment period, repeat exercise treadmill testing and 48-hour AECG monitoring were performed.

Patient Population

A group of 194 patients from eight institutions were screened for participation in the study. A total of 63 eligible patients received randomized treatment; of these, seven discontinued participation after completing less than two double-blinded treatment periods (one because of death, five because of the development of unstable angina or acute myocardial infarction, and one because of an orthopedic problem) and were, therefore, not available for analysis of comparative efficacy. Of the 56 patients who completed two or more double-blinded treatment periods, 42 were men and 14 women, with a mean age (±SD) of 60.1±8.1 years. The mean duration of angina before randomization was 60±58 months. Thirty-three patients (52%) had experienced a prior myocardial infarction, and 21 (38%) had a previous revascularization procedure (coronary artery bypass surgery or percutaneous transluminal coronary angioplasty). Other patient characteristics have been described in detail previously.13 Six patients were excluded because of major protocol violations. The remaining 50 patients who were treated with each of the four treatments and who had complete AECG monitoring performed at the end of each treatment period constitute the study population for this data base study.

AECG Monitoring

AECG monitoring was performed with Applied Cardiac Systems cassette recorders (Laguna Hills, Calif) and modified leads V1 and aVF, and ECGs were analyzed on a CardioData MK4 playback system with modified software.14,15 An ischemia episode was defined as transient ischemic ST segment depression of at least 1.0 mm, lasting at least 1.0 minute, and separated from other episodes by at least 5.0 minutes. Minute-by-minute heart rate was identified throughout the recording session.

Heart Rate Analyses

Heart rate activity preceding each episode of ischemia. To determine the general pattern of heart rate changes, the mean minute-by-minute heart rate was calculated for the hour preceding and the hour following the onset of each ischemic episode.

Magnitude and duration of heart rate changes throughout the 48-hour AECG recording. The minute-by-minute heart rate throughout the entire 48-hour AECG recording was determined for each individual patient during each treatment phase. To minimize transient or physiologically insignificant heart rate variability, each minute’s heart rate value was calculated as the mean of that minute’s heart rate as well as the 2 adjacent minutes on either side of that minute. To identify the presence of a period of heart rate increase, the heart rate for each minute was compared with the heart rate 5 minutes earlier, and this “moving window” was advanced in
1-minute increments for the entire 48-hour monitoring period. The computer algorithm was designed to detect and categorize episodic heart rate changes of variable absolute magnitude, allowing each set of analyses to be repeated with different definitions for a "significant heart rate increase." The baseline heart rate for each period of heart rate increase was defined as the heart rate value that immediately preceded the heart rate increase 5 minutes before episode onset. The end of the period of heart rate increase was defined as the time at which heart rate fell to a level at which the elevation above baseline heart rate no longer met the definition of a significant heart rate increase or the time at which the heart rate fell by at least 50% of the difference between its peak elevation and its baseline. Having identified periods of significant heart rate increase, we were able to calculate the percentage of such periods that were accompanied by ischemia under various sets of conditions.

**Classification of an ischemic episode during a period of increased heart rate.** To identify episodes of ischemia with potentially different pathophysiological origins, each episode of ischemia was categorized as occurring during a period of increased heart rate (type 1), occurring 0-10 minutes after a period of increased heart rate (type 2), or occurring in the absence of a heart rate increase (type 3).

**Likelihood of development of an ischemic episode.** The likelihood for a period of heart rate increase to be associated with an episode of ischemia was calculated for various different magnitudes of heart rate increase, duration of heart rate increase, and baseline heart rates before the increase in heart rate.

**Analysis of Circadian Variation.**

The frequency distribution of the time of onset of ischemic episodes was plotted for all episodes and then separately for episodes associated with and those not associated with a heart rate increase. The data were plotted over a 24-hour period in predefined 3-hour time blocks beginning with midnight. The circadian distributions of episodes were compared across the different treatment regimens.

**Statistical Methods.**

Mean heart rate was compared with baseline by a correlated *t* test. Comparisons were made between the proportion of heart rate increases associated with episodes of ischemia after various magnitudes and durations of heart rate increases, starting at various baseline heart rates, and on different therapies by the χ² test. For analyses of circadian variation, the χ² test for goodness of fit was used to determine whether a circadian pattern existed, and comparisons were made between the circadian patterns on the different treatment regimens by a χ² test. Two-sided *P* < .05 was considered significant.

A multivariate logistic analysis was performed to test whether a circadian pattern existed for the occurrence of episodes of ischemia independent of circadian changes in heart rate parameters, to determine whether the various heart rate parameters exerted mutually independent effects on the likelihood of development of ischemia, and to determine whether medication affected the circadian pattern of ischemic episodes. The predictors of ischemia used in the model included 1) continuous variables indicating the magnitude of heart rate increase, duration of heart rate increase, and baseline heart rate 5 minutes before heart rate increase; 2) indicators for the time of day at which the heart rate increase occurred; and 3) indicators corresponding to the medication on which the heart rate increase occurred. Because each patient displayed multiple episodes of heart rate increases throughout each monitoring period, an adjustment for repeated measures was included in the multivariate analysis.

**Results**

**General Heart Rate Pattern Preceding Ischemia.**

When the minute-by-minute heart rate during the hour preceding episodes of ischemia was analyzed, the mean heart rate showed no significant deviation until a significant increase was observed beginning 6 minutes before the onset of ischemia. This increase reached a peak with a mean ± SEM of 12.6 ± 0.6 beats per minute above a baseline value taken 5 minutes before the onset of ischemia, with the peak coinciding with the onset of ischemia. When the minute-by-minute heart rate preceding ischemia was analyzed separately for episodes occurring in the four treatment arms, a similar absolute increase in mean heart rate was observed (placebo, 12.9 ± 1.4 beats per minute; propranolol, 12.3 ± 1.4 beats per minute; diltiazem, 11.2 ± 1.5 beats per minute; nifedipine, 12.0 ± 1.4 beats per minute; *P* > .05), although the values for baseline heart rate preceding ischemia were different among the four therapies (placebo, 82.0 ± 1.5 beats per minute; propranolol, 65.9 ± 1.7 beats per minute, *P* < .0001 compared with placebo; diltiazem, 78.5 ± 1.6, *P* < .01 compared with placebo; and nifedipine, 83.9 ± 1.6 beats per minute, *P* > .05 compared with placebo).

**Magnitude and Duration of Daily Heart Rate on Each Therapy.**

Figure 1A displays the frequency of the occurrence of periods of heart rate increases of various magnitudes during each of the four treatment arms, using 400 patient-days of AECG monitoring. Most periods (57%) of increased heart rate were < 10 beats per minute in magnitude. While receiving propranolol therapy, patients experienced a threefold reduction in the frequency of heart rate increases ≥ 15 beats per minute compared with heart rate activity on the other three therapies (*P* < .001). There was no important difference in the frequency of heart rate increases among the other three therapies. Likewise, most periods (70%) of increased heart rate were < 10 minutes long (Figure 1B). During propranolol therapy, patients experienced a 40% reduction in the frequency of periods of increased heart rate that were ≥ 20 minutes long compared with the other therapies (*P* < .001), whereas there was no difference in the duration of heart rate increases among the other therapies. Furthermore, the baseline heart rate before heart rate increases was markedly lower during propranolol therapy compared with other therapies: during propranolol therapy, 88% of periods of heart rate increase started at a baseline < 70 beats per minute, whereas on the other three therapies, the baseline heart rate was more evenly distributed between 60 and 90 beats per minute (*P* < .001) (Figure 1C).
Heart rate increases of increasing magnitude are plotted on the abscissa, with the absolute number of such episodes of heart rate increases occurring during the 400 patient-days of ambulatory monitoring plotted on the ordinate. Compared with placebo, therapy with propranolol was associated with fewer periods of heart rate increases of $>10$ beats per minute (bpm) ($P<.05$).

Panel B: Distribution of periods of heart rate increases of various durations by treatment group. Heart rate increases of increasing duration are plotted on the abscissa, with the absolute number of such periods of heart rate increase occurring during the 400 patient-days of ambulatory monitoring plotted on the ordinate. For all durations of periods of heart rate increase, there were fewer episodes on propranolol therapy compared with placebo ($P<.001$).

Panel C: Distribution of periods of heart rate increases by treatment group and increasing baseline heart rate. Heart rate increases that started at increasing baseline heart rate are plotted on the abscissa, with the absolute number of such periods of heart rate increases occurring during 400 patient-days of ambulatory monitoring plotted on the ordinate. Compared with placebo, therapy with propranolol was associated with fewer periods of heart rate increases of $>10$ beats per minute (bpm) ($P<.05$).

**Classification of Ischemic Episodes by Type and Treatment Group**

Of the 951 episodes of ischemia in our data base, there were sufficient heart rate data to categorize 933 episodes by the temporal relation of episode onset to periods of heart rate increase. Of these 933 ischemic episodes, 758 (81%) were temporally associated with periods of increased heart rate (type 1, 682 episodes [73%]; type 2, 76 episodes [8%]) and 175 episodes (19%) were not associated with periods of heart rate increase (type 3). Every patient experienced type 1 episodes, 68% of patients experienced type 2 episodes, and 68% of patients experienced type 3 episodes. In seven patients (14%), more than 33% of the episodes were type 3 (maximum percentage, 60%), and these seven patients accounted for 47% of type 3 episodes (83 of 175 episodes).

As previously reported, only propranolol resulted in a significant overall decrease in the absolute number of episodes of ischemia compared with placebo, whereas diltiazem therapy was associated with a trend toward a decrease in episodes. However, as shown in Table 1, when the efficacy of the four therapies was analyzed by episode type, active medications exerted different effects on episodes associated with heart rate increases (types 1 and 2) and those not associated with heart rate increases (type 3). Compared with placebo, propranolol was more effective in suppressing types 1 and 2 episodes (65% reduction) than type 3 episodes (45% reduction, $P=.05$). In contrast, compared with placebo, nifedipine reduced types 1 and 2 episodes by only 27% but caused a marked 58% reduction of type 3 episodes ($P=.02$). Diltiazem therapy resulted in a 35% reduction in types 1 and 2 episodes, with a 43% reduction in type 3 episodes ($P>.5$). The distribution of the proportion of residual ischemic episodes by episode type and treatment group is shown in Figure 2. Propranolol was associated with a higher proportion of residual ischemia that was non–heart rate related (type 3), whereas nifedipine was associated with a lower proportion of such episodes.

**Likelihood of Developing an Ischemic Episode**

As shown in Figure 3, the overall likelihood of a patient’s developing ischemia associated with a period of increased heart rate on any of the drug treatments was proportional to both the absolute magnitude of the heart rate increase and the duration of the increased heart rate. For example, there was a 4% likelihood of developing ischemia after a heart rate increase of 5-9 beats per minute lasting $<10$ minutes, whereas there was a 60% likelihood of developing ischemia after a heart rate increase $\geq 20$ beats per minute lasting $\geq 40$ minutes. Similarly, as shown in Table 2, the level of
baseline heart rate before a heart rate increase was directly proportional to the likelihood of developing ischemia ($P<.001$). The likelihoods of developing ischemia based on magnitude or duration of heart rate increases or the level of baseline heart rate were similar on each of the four medication treatments.

Multivariate analysis indicated that the magnitude of the heart rate increase and the baseline heart rate before the increase in heart rate made strong and mutually independent contributions to predicting the probability of ischemia ($\chi^2$, 454 and 123, respectively; each, $P<.001$), but the duration of heart rate increase was less predictive ($\chi^2$, 4.0; $P=.05$) (Table 3).

**Circadian Distribution of Episodes of Ischemia**

As shown in Figure 4, ischemic episodes associated with an increase in heart rate (types 1 and 2) displayed a marked circadian distribution ($\chi^2$, 103.5; $P<.001$) with a peak between 6 and 9 AM, and the overall frequency remained high throughout the waking hours. In contrast, episodes not associated with periods of increased heart rate (type 3) did not display a significant circadian variation. Between the hours of midnight and 6 AM, a much higher proportion of the total ischemic episodes was type 3 (39%) compared with episodes occurring between 6 AM and midnight (15%). The circadian distributions of all three types of ischemic episodes were similar on each of the active therapies compared with placebo. As shown in Figure 5, there was a close parallel circadian distribution of periods of increased heart rate not associated with ischemia and those periods associated with ischemia.

To determine whether the likelihood of developing ischemic episodes varied throughout the day, heart rate parameters alone were first added to the multivariate model predicting the likelihood of developing ischemia, followed by the addition of time of day in 3-hour bins. As shown in Table 3, only the heart rate variables (magnitude and duration of heart rate increase and baseline heart rate) influenced the likelihood of developing ischemia, whereas the time of day per se had no significant independent effect, indicating that observed differences associated with circadian patterns in univariate analyses are explainable by changes in these heart rate variables alone.

**Multivariate Analysis of Effect of Anti-Ischemic Therapy on Ischemic Episodes**

The effect of therapy with diltiazem, nifedipine, or propranolol was also added to the multivariate model predicting the likelihood of developing ischemia so as to determine whether therapy with any of the medications influenced the likelihood of developing ischemia beyond the effects of the medications on the heart rate parameters (Table 3). Nifedipine therapy was associated with a lower likelihood of the development of ischemia after all heart rate parameters were controlled for, suggesting an anti-ischemic effect resulting from the prevention of coronary vasoconstriction. In contrast, despite the marked overall anti-ischemic effect of propranolol, there was a trend toward an increased likelihood of developing ischemia after its effects on heart rate parameters were controlled for. Diltiazem’s anti-ischemic efficacy in our model appeared to be primarily a result
TABLE 2. Likelihood of Developing Ischemia After Heart Rate Increases Starting at Different Baseline Heart Rates

<table>
<thead>
<tr>
<th>Baseline heart rate (bpm)</th>
<th>Likelihood of ischemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>8.7</td>
</tr>
<tr>
<td>60-70</td>
<td>10.4</td>
</tr>
<tr>
<td>70-79</td>
<td>14.3</td>
</tr>
<tr>
<td>80-89</td>
<td>16.6</td>
</tr>
<tr>
<td>≥90</td>
<td>18.5</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.

of its effects on heart rate parameters, with no additional effect detected by the multivariate analysis.

Discussion

A refined understanding of the pathophysiology of ambulatory ischemia is important because it may facilitate the selection of anti-ischemia medications and because it may provide insights into the processes responsible for ischemia, perhaps even for myocardial infarction and sudden death. Our results indicate that >80% of episodes of ambulatory ischemia are associated with substantial increases in heart rate. Moreover, the likelihood of developing ischemia can be clearly estimated by identification of the magnitude and duration of a heart rate increase and the baseline heart rate before the increase. Time of day per se does not seem to influence the likelihood of developing ischemia other than providing a time frame within which increases in heart rate occur. These relations between heart rate variables and the development of ischemia explain why agents such as propranolol are so effective at suppressing ischemia: β-blockers reduced the baseline heart rate as well as the magnitude and duration of heart rate increases occurring throughout the day. Our data also suggest that there may be a differential anti-ischemic effect among the specific agents on the episodes not associated with an increase in heart rate: propranolol was significantly less effective in treating such episodes compared with nifedipine.

TABLE 3. Multivariate Analysis of Variables Predictive of Developing an Ischemic Episode After a Period of Heart Rate Increase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized estimate</th>
<th>Wald χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnitude of heart rate increase</td>
<td>-0.56</td>
<td>473.9</td>
<td>.0001</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>-0.45</td>
<td>123.2</td>
<td>.0001</td>
</tr>
<tr>
<td>Duration of heart rate increase</td>
<td>-0.04</td>
<td>4.0</td>
<td>.05</td>
</tr>
<tr>
<td>Time of day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 AM-9 AM</td>
<td>0.03</td>
<td>0.9</td>
<td>.35</td>
</tr>
<tr>
<td>9 AM-12 noon</td>
<td>0.05</td>
<td>2.2</td>
<td>.14</td>
</tr>
<tr>
<td>12 noon-3 PM</td>
<td>0.01</td>
<td>0.1</td>
<td>.70</td>
</tr>
<tr>
<td>3 PM-6 PM</td>
<td>0.06</td>
<td>3.0</td>
<td>.08</td>
</tr>
<tr>
<td>6 PM-9 PM</td>
<td>-0.02</td>
<td>0.5</td>
<td>.49</td>
</tr>
<tr>
<td>9 PM-12 midnight</td>
<td>-0.01</td>
<td>0.1</td>
<td>.74</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.03</td>
<td>0.9</td>
<td>.36</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.12</td>
<td>19.4</td>
<td>.0001</td>
</tr>
<tr>
<td>Propranolol</td>
<td>-0.10</td>
<td>6.7</td>
<td>.01</td>
</tr>
</tbody>
</table>

Heart Rate Patterns Preceding Episodes of Ischemia

Although heart rate alone is an incomplete gauge of myocardial oxygen demand, it is a useful and feasible method to identify changes in demand, because changes in ambulatory heart rate and systolic blood pressure generally parallel each other very closely. Some investigators have observed that the majority of ambulatory ischemic episodes are preceded by an increase in heart rate,9–11 whereas others observe that most episodes occur in the absence of an increase in heart rate and, presumably, are caused by episodic vasoconstriction.1,2,12 However, there has not been uniformity in the criteria used to gauge an increase in heart rate before an episode: some investigators compare the heart rate at the onset of ischemic ST segment depression with the heart rate 2-5 minutes earlier,3,10,16,17 whereas others compare it with the heart rate 15 minutes before the onset of ST segment depression2 or to the mean heart rate during the hour before the episode.11 The present study provides a more thorough dissection of the role of heart rate increases in the pathogenesis of ischemia by disclosing a complete profile of heart rate changes throughout the day, providing a "denominator" with which the "numerator" of ischemic episodes can be compared. We also use continuous values of heart rate variables not previously studied: the magnitude and the duration of heart rate increases and the baseline heart rate preceding an increase in heart rate. A composite of these heart rate variables allows for a quantitative estimate of the likelihood of developing ischemia. Our data also suggest that the baseline heart rate is important in determining whether ischemia occurs in association with a heart rate increase, probably because an elevated baseline heart rate is nearer the ischemic threshold than a lower baseline heart rate.

We also categorized ischemic episodes associated with an increase in heart rate into two types based on the temporal association between the increase in heart rate and the onset of ischemia. The vast majority of ischemic episodes were those associated with a heart rate increase immediately preceding ischemia (type 1). A minority of heart rate–associated episodes were those in which ischemia developed within 10 minutes of the decline in heart rate after a preceding increase (type 2); these were considered related to the prior heart rate increase because ST segment depression may be a late manifestation of ischemia, similar to the ischemic ST segment depression that may occur only in the recovery phase after an exercise test.18 These episodes occurring after the increase in heart rate would have been classified as not related to an increase in heart rate according to previous categorization schemes based only on a single heart rate value before the onset of ischemia. Because of small numbers, we were not able to analyze the characteristics of type 2 episodes separately. Future application of our classification scheme to larger data bases may provide more information about these type 2 episodes.

Effect of Medications on the Different Types of Episodes of Ischemia

We hypothesized that propranolol, because of its marked effects on lowering heart rate, may be more effective in suppressing types 1 and 2 ischemic episodes,
whereas diltiazem and nifedipine, because of their potent coronary vasodilating properties, may be particularly effective at suppressing the type 3 episodes. If these two hypotheses were correct, the distribution of "residual" episodes of ischemia on the different medications should reflect these differential effects. Indeed, we found that propranolol therapy was associated with a higher proportion of type 3 episodes and nifedipine a lower proportion of type 3 episodes compared with placebo. Further support for our hypothesis comes from the results of our multivariate analysis, which indicated that propranolol was effective entirely by reducing heart rate variables (Tables 1 and 2; Figure 1). In fact, after these heart rate parameters were adjusted for, propranolol therapy was associated with an actual increased likelihood of developing ischemia, perhaps reflecting blockade of \( \beta_2 \)-receptors leading to a predisposition to coronary vasoconstriction. The decreased heart rate threshold at the onset of ischemia that we observed in this study during propranolol therapy compared with the other forms of therapy adds further support to the concept that propranolol may lead to heightened coronary vasoconstriction. In contrast, although nifedipine had no overall effect of reducing ischemic episodes, it was associated with a significant, albeit minor, effect of preventing those episodes presumably caused by vasoconstriction. Diltiazem's anti-ischemic efficacy appeared to be related primarily to a reduction in heart rate parameters, similar to the effects of propranolol but to a lesser degree. It is not clear why diltiazem did not also reduce type 3 episodes, but the lack of observed benefit on these episodes may be a result of their small number in our study.

**Circadian Distribution of Ischemic Episodes**

Our results confirm the morning increase of episodes of ambulatory ischemia observed by others, but we provide the additional unique information that this pattern occurs only in episodes associated with a heart rate increase (types 1 and 2). Quyyumi and colleagues reported that the ischemic threshold is lower and post-ischemic forearm vascular resistance higher in the morning (8 AM) and at night (9 PM) compared with noon and 5 PM, and we anticipated that the likelihood of developing ischemia at these times would be increased for any given increase in heart rate. However, our multivariate analyses (Table 3) demonstrated that the likelihood of developing ischemia was entirely ac-

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**Figure 4.** Graph showing circadian distribution of types 1 and 2 versus type 3 episodes of ischemia. Time is plotted on the abscissa with a 24-hour clock, with the absolute number of episodes of ischemia plotted on the ordinate. Each time plotted on the abscissa represents a 3-hour time block starting at the designated hour. The 24-hour pattern is replotted for a second 24 hours to facilitate recognition of the circadian patterns. There was a significant increase in the occurrence of types 1 and 2 episodes during the daytime hours between 6 AM and 9 PM (P<.01). In contrast, there was no circadian variation of type 3 episodes.

**Figure 5.** Graph showing circadian distribution of periods of heart rate increase associated with episodes of ischemia and distribution of total periods of heart rate increase. Time is plotted on the abscissa with a 24-hour clock, with the absolute number of episodes of ischemia plotted on the ordinate. Each time plotted on the abscissa represents a 3-hour time block starting at the designated hour. The 24-hour pattern is replotted for a second 24 hours to facilitate recognition of the circadian patterns.
counted for by changes in heart rate alone, without an independent effect of time of day. The differences in results may be caused by differences in methodology: the observations by Quyyumi et al\textsuperscript{24} are based on the ischemic threshold on a supervised exercise test, whereas our observations are based on AECG monitoring during unrestricted daily activities.

It is also interesting that ischemic episodes occurring without an increase in heart rate (type 3) appeared to have a nearly even distribution throughout the day and night. We expected that these episodes would have an increased incidence in the morning and night because of the increased vascular resistance at these times.\textsuperscript{24} Although we did not observe such an increase in our small sample of these episodes, we did observe that they were present throughout the day. This pattern of occurrence may suggest that episodes of coronary vasoconstriction may occur at different times of the day, some perhaps related to more endogenous circadian patterns\textsuperscript{24} and others related to external stimuli such as mental stress or cigarette smoking.\textsuperscript{5,8,26,27} More definitive conclusions concerning these episodes must await exploration of larger data bases.

Limitations
There are three important limitations to this study. The first limitation is that heart rate activity alone was used to categorize ischemic episodes and to suggest pathophysiological mechanisms. Such a technique ignores other important determinants of myocardial oxygen demand, as described earlier. Second, our findings represent a post hoc analysis of a preexisting data base. Hence, our results must be considered to be hypothesis-generating until this analysis is validated in other data bases. Finally, because of the relatively small numbers of types 2 and 3 episodes observed in our study, application of our classification scheme to larger data bases may yield new information regarding the circadian patterns of these two types of episodes and their response to treatment.

Clinical Implications
The results observed in this study are important for two reasons. First, in a large population of patients with chronic stable angina, most episodes of ischemia are associated with increases in a number of heart rate variables. These observations explain why therapies that reduce the magnitude and duration of heart rate increases and reduce baseline heart rate are effective in preventing ischemia. Second, in this same group of patients, there is a subgroup of episodes not associated with heart rate increases that may be caused by coronary vasoconstriction; these episodes are more effectively treated by nifedipine than by propranolol. It is possible that combination therapy with a $\beta$-adrenergic blocker and a calcium channel antagonist may be more effective than single-agent therapy for the total suppression of all types of ambulatory ischemia\textsuperscript{28,29} and thereby confer more widespread protection against adverse cardiac events.

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