Relations Between Heart Rate, Ischemia, and Drug Therapy During Daily Life in Patients With Coronary Artery Disease

James M. McLenachan, MD; Franz F. Weidinger, MD; Joan Barry, BA; Alan Yeung, MD; Elizabeth G. Nabel, MD; Michael B. Rocco, MD; and Andrew P. Selwyn, MD

Background. Previous studies have shown that little if any increase in heart rate occurs 1 minute before the onset of ischemia in ambulant patients with coronary artery disease. This study tested the hypothesis that there are characteristic relations between heart rate and ischemia in ambulant patients with coronary artery disease.

Methods and Results. Twenty-one patients with proven coronary disease demonstrated 212 episodes of ischemia during 504 hours of continuous monitoring of the electrocardiogram. An important increase in heart rate (from 74±11 to 90±14 beats/min, p<0.001) occurred between 5 and 30 minutes (not 1 minute) before the onset of ischemia. A significantly higher heart rate at onset of ischemia was seen during Bruce protocol exercise testing than during daily life (117±12 versus 95±15 beats/min, p<0.01). However, when a less-strenuous, but more prolonged, exercise protocol was used in a subgroup of patients (n=12), ischemia occurred at a heart rate that was significantly lower than during the Bruce protocol (88±14 versus 103±15 beats/min, p<0.05) and was not significantly different from the threshold heart rate at onset of ischemia during daily life (88±14 versus 84±12 beats/min, p=NS). As part of two placebo-controlled trials, treatment with both propranolol and nitroglycerin altered the distribution of ischemic events by heart rate but in opposite directions. Although propranolol largely eliminated events occurring at high (>100 beats/min) and moderate (80–100 beats/min) heart rates, the number of events at low (<80 beats/min) heart rates was increased. In contrast, nitroglycerin reduced episodes at low and moderate heart rates only.

Conclusions. Important increases in heart rate occur before the onset of ischemia during daily life, but this increase occurs much earlier than has been reported. Duration of heart rate increase appears to influence the heart rate threshold for ischemia, and this may contribute to the occurrence of ischemia at lower heart rates during daily life than during standard exercise testing. Last, different classes of drugs appear to have characteristic effects on ischemia occurring at different heart rates that may be useful in planning therapy. (Circulation 1991;83:1263–1270)

Ambulatory monitoring of the electrocardiogram (ECG) has provided an opportunity to study transient myocardial ischemia in patients with coronary artery disease while unrestrained and busy during daily life.1–3 Although most ischemic events are asymptomatic,3–5 several studies have shown that such evidence of ischemia is an independent predictor of increased risk.6–8 Many studies have also shown that transient myocardial ischemia in ambulant patients occurs with little or no increase in heart rate and at heart rates significantly lower than those during exercise testing.2,4,9–11 To understand the relation between heart rate and ischemia, most studies have examined events 1 minute before onset of ST segment depression; none has compared heart rate at onset of ischemia with the heart rate at various time intervals or during all nonischemic periods of the day. In addition, the relation between heart rate and ischemia has not previously been examined in patients taking different classes of antianginal drugs, which have widely varying effects on heart rate and on the activity of ischemic heart disease as viewed by ambulatory monitoring.12–15
The aims of this study were to examine heart rate at a range of time intervals before the onset of ischemia and to compare them with the nonischemic heart rate throughout the day to test the hypothesis that significant and important increases in heart rate occur before ischemic events. We studied different exercise protocols to test the hypothesis that the duration of increase and the magnitude of increase in heart rate are both important and can explain why ischemia during daily life can occur at lower heart rates than are seen during standard Bruce protocol exercise testing.

Last, we examined the effects of a β-adrenergic receptor blocker and a transdermal nitrate to test the hypothesis that these drugs have individual effects on ischemia occurring at different heart rate thresholds, which suggest different mechanisms of action.

**Methods**

**Patients**

One hundred five patients with clinical manifestations of coronary artery disease and positive exercise tolerance tests underwent ambulatory ECG monitoring between December 1984 and May 1988 at the Brigham and Women’s Hospital. Antianginal medications were withdrawn 48 hours before the study, with the exception of nitroglycerin, use of which was permitted both before and during monitoring. Of the 105 patients, 69 had positive evidence of transient myocardial ischemia during ambulatory ECG monitoring. To study the relation between heart rate and ischemia, patients were included in this analysis if they demonstrated at least four episodes of significant ST depression (defined below) during a 24-hour monitoring period. The study group comprised 21 patients (group 1). There were no significant differences between the 21 patients selected and the 69 making up the total group with regard to age, sex, angina class, exercise test parameters, and history of previous myocardial infarction. The study group, however, did have a higher prevalence of three-vessel disease compared with those patients with positive evidence of ischemia but with less than four episodes during 24-hour recording (50% versus 29%, p<0.05).

Three additional analyses were performed. Twelve patients (11 men and 1 woman), with a mean age of 54 years (range, 36–70 years) underwent two treadmill exercise tests as described below (group 2). Eight male patients with a mean age of 57 years (range, 36–75 years), participated in a double-blind, placebo-controlled, randomized crossover study examining the effects of propranolol (120 mg/day) on the frequency and characteristics of out-of-hospital ischemia (group 3a). An additional eight male patients with a mean age of 60 years (range, 36–75 years) participated in a study examining the effects of transdermal nitroglycerin (30–60 mg/24 hr) on out-of-hospital ischemia (group 3b). The principal results of these two intervention studies have been published elsewhere; data included in this analysis relate only to the effects of drug treatment on heart rate at onset of ischemia in subgroups of the original studies.

**Ambulatory ECG Monitoring**

Twenty-four-hour ECG recordings were made on all patients in group 1 (n=21). Patients in groups 3a (n=8) and 3b (n=8) underwent 24-hour recording during placebo and propranolol (group 3a) and nitroglycerin (group 3b) administration. Recordings were made with a calibrated frequency-modulated recorder (Oxford Instruments North America Inc., Bedford, Mass.). Bipolar leads were attached with the exploring electrodes positioned at the site of the most positive leads during exercise testing, usually the standard V₃ and modified inferior positions. Patients were instructed to engage in normal daily activities and to record any symptoms and the amount of nitroglycerin consumed.

All tapes were analyzed visually at 60 times real time with a Cardiodata Mark IV analyzer. An episode of significant ST depression was defined as planar horizontal or downsloping ST segment depression of 0.1 mV or greater persisting 0.08 seconds beyond the J point and lasting for at least 60 seconds in consecutive complexes. A separate episode was recorded only if the ECG had returned to baseline for at least 3 minutes. All tapes were read by two independent, experienced readers. For each patient, we recorded the total number of episodes, the duration of each episode, and the presence or absence of symptoms.

For the calculation of nonischemic heart rate (see below), mean heart rate for every minute of the entire 24-hour record (group 1) was printed using a software program (CARDIODATA). Mean heart rate for each 5-minute period of the 24-hour record was then calculated from the minute-by-minute printout. To calculate heart rate for the nonischemic portion of the day, all 5-minute periods in which an episode of ischemia had occurred were then excluded. Because other manifestations of ischemia, including disturbed myocardial metabolism and left ventricular dysfunction exceed the duration of ST segment depression, the heart rate values from a 10-minute period both immediately before and after each episode were also excluded. In addition, heart rate at 30, 15, 10, and 5 minutes before each ischemic event was calculated.

**Exercise Testing**

All 21 patients in group 1 underwent one symptom-limited treadmill exercise test according to a Bruce protocol. ECGs were recorded at the start of exercise, every minute thereafter, at the onset of chest pain, and at peak exercise. Duration of exercise, time to 1 mm ST depression, and heart rate at 1 mm ST depression were recorded for each patient.

The 12 patients in group 2 underwent two additional exercise tests, one after the standard Bruce protocol and one after a less-intense protocol that was identical to the modified Bruce protocol except that stage 1 was continued for 6 minutes instead of 3.
The aim of this protocol was to ensure a longer duration of less-strenuous exercise than during a standard Bruce protocol. The two tests were performed in randomized order, on the same day, and at least 2 hours apart. As before, treadmill time, time to 1 mm ST depression, and heart rate at 1 mm ST depression were recorded for each patient.

Statistical Analysis

Because the nonischemic heart rate values were not normally distributed, the median nonischemic heart rate was calculated for each patient. When comparing patients, however, the median heart rate values (one per patient) were normally distributed. Thus, differences between heart rate at onset of ischemia and nonischemic heart rate were assessed by a paired t test.

A median heart rate value for each time period (−30, −15, −10, and −5 minutes) before the onset of ST segment depression for each ischemic event was derived. Because all patients had multiple episodes of ischemia, a single median value was then derived for each time point from each of the 21 patients. These values were normally distributed. A repeated measures analysis of variance, incorporating baseline (nonischemic) heart rate, heart rate at 30, 15, 10, and 5 minutes before ST depression, and heart rate at the onset of 1 mm ST depression, was performed to determine the significance of heart rate changes during the period leading up to ischemia. To determine the time at which the increase in heart rate from baseline first became significant, nonischemic heart rate was compared with the heart rate at each time interval before the onset of ischemia by means of a paired t test. Because five comparisons were made (baseline versus 30, 15, 10, 5, and 0 minutes before ischemia), significance was assumed at a probability level of 0.01 (Bonferroni’s correction).

Differences in exercise test variables (exercise time, time to 1 mm ST depression, and heart rate at 1 mm ST depression) were analyzed by a two-tailed t test for paired data, and significance was assumed at a probability level of 0.05.

To evaluate treatment effects with β-blocker and nitrate, ischemic episodes detected by 24-hour monitoring during treatment with placebo and propranolol (group 3a) and transdermal nitroglycerin and matching placebo (group 3b) were categorized into those occurring at heart rates less than 80 beats/min, 80–100 beats/min, and greater than 100 beats/min. The distributions of episodes in each heart rate category for the two active treatments (propranolol and nitroglycerin) were compared by a χ2 test, and significance was assumed at a probability level of 0.05. All data are expressed as mean±SD unless otherwise stated.

Results

Patient Characteristics

Twenty-one subjects (19 men and two women) (group 1) each demonstrated four or more episodes

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>NYHA class</th>
<th>Previous MI</th>
<th>Diseased vessels (n) (&gt;70% stenosis)</th>
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NYHA class, New York Heart Association class (angina); MI, myocardial infarction; IMI, inferior myocardial infarction; AMI, anterior myocardial infarction.
of ischemia during ambulatory ECG monitoring. Their baseline data are summarized in Table 1. Mean age for the study group was 59±3 years (range, 36–75 years). Eight patients (38%) were classified as New York Heart Association class I, nine (43%) as class II, and four (19%) as class III. Eleven patients (52%) had ECG evidence of myocardial infarction. The diagnosis of coronary artery disease was confirmed angiographically in 18 (86%); the remaining patients had unequivocal evidence of previous myocardial infarction.

**Ambulatory SCG Monitoring**

Two hundred twelve ischemic episodes were detected in 21 patients forming the study group (group 1). The median number of episodes per patient was 11 (range, 4–30), and the median duration of a single episode was 5 minutes (range, 1–72 minutes). Thirty-five episodes (17%) were accompanied by chest pain, the remainder being asymptomatic.

**Ischemic Threshold During Ambulatory ECG Monitoring**

Figure 1 illustrates the range of nonischemic heart rates (open boxes) during 24-hour ambulatory ECG monitoring of 21 patients (group 1). Also shown is the heart rate at onset of each ischemic episode (open circles). Although most patients demonstrated ischemia throughout a range of heart rates, most events in most patients occurred toward the upper end of the heart rate range for that patient. This is illustrated in Figure 2, which shows the heart rate distribution for the entire 24-hour period for a single patient (open boxes). Although the patient experienced 11 ischemic episodes throughout a range of heart rates (filled boxes), most events tended to occur at a heart rate greater than the median nonischemic heart rate.

The data for all 21 patients are summarized in Figure 3. For each patient, heart rate at onset of ischemia was higher than the nonischemic heart rate; for the group as a whole, the difference was highly significant (95±15 versus 74±11 beats/min, *p<0.01*).

Figure 4 examines the time course of the increase in heart rate before ischemia. Analysis of variance demonstrated a significant change in heart rate over time (*p<0.001*). Heart rate 30 minutes before ischemia was not significantly different from the nonischemic heart rate. At 15 minutes before onset of ischemia, however, heart rate was already higher than the nonischemic heart rate (85±13 versus 74±11 beats/min, *p<0.001*). At 10 and 5 minutes before ST depression, heart rate continued to rise higher than the nonischemic value (87±13 versus 74±11 beats/min, *p<0.001*, and 90±14 versus 74±11 beats/min, *p<0.001*, respectively) (Figure 4). Although heart rate did rise further in the 5 minutes immediately before ischemia, it is noteworthy that 75% of the total rise in heart rate before ischemia occurred more than 5 minutes before the onset of ST depression (Figure 4).

**Influence of Magnitude and Duration of Heart Rate Increase on Ischemic Threshold**

To further examine the relation between the duration and intensity of changes in heart rate and ischemia, two further analyses were undertaken.
FIGURE 4. Plot of mean heart rate (shown in graph and numerical form) plus standard deviations during the nonischemic portion of the day (baseline) and at 30, 15, 10, 5, and 0 (onset) minutes before ischemia. Analysis of variance demonstrated a highly significant change over time (p<0.001). Comparison of each time point with baseline heart rate showed that this rise first became significant 15 minutes before the onset of ischemia. *p<0.01 and **p<0.001, difference from baseline nonischemic heart rate.

1. During ambulatory ECG monitoring. For each patient, the ischemic event occurring at the lowest heart rate was identified. The number of episodes during the whole recording period during which this heart rate was sustained or exceeded for a period of at least 5 minutes, whether or not this was accompanied by ischemia, was then calculated, and the magnitude and duration of each episode of heart rate increase (in minutes) were determined.

In total, 268 episodes were identified in which heart rate increased above the lowest heart rate that produced ischemia in that patient. Of these episodes, 144 were accompanied by ischemia and 124 were not. The episodes of increased heart rate associated with ischemia showed an absolute heart rate of 96.2±13.0 beats/min at onset of ischemia, whereas the episodes not associated with ischemia showed an absolute increase in heart rate to 97.9±15.5 beats/min (p=NS). In contrast, the median duration of those episodes that did not produce ischemia was 7.5 minutes compared with 35 minutes for those episodes that were accompanied by ischemia (p<0.001 by Mann-Whitney U test).

The distributions of duration of episodes of increased heart rate with and without ischemia are shown in Figure 5.

2. During exercise testing. During the standard Bruce protocol, mean exercise time for the 21 patients in group 1 was 5.2±2.4 minutes, and mean time to ischemia was 2.7±1.3 minutes. Mean heart rate at onset of 1 mm ST depression during treadmill testing was 117±12 beats/min and was significantly higher than the mean heart rate at onset of ischemia during ambulatory ECG monitoring (117±12 versus 95±15 beats/min, p<0.01). Twelve patients (group 2) subsequently performed two exercise tests following different protocols. Baseline values before exercise were similar (Table 2), and all patients developed at least 1 mm of ST segment depression during both tests. On the modified protocol, total exercise time was significantly greater (12.6±6.8 versus 5.5±2.3 minutes, p<0.05), and time to onset of 1 mm ST segment depression was prolonged from 3.0±1.2 to 5.7±1.8 minutes (p<0.01) compared with that on the Bruce protocol. When ischemia occurred, however, it did so at a lower heart rate during the modified protocol than during the Bruce protocol (88±14 versus 103±15 beats/min, p<0.05) (Table 2). The lower heart rate at onset of ischemia during the modified exercise test was not significantly different from the heart rate at onset of ischemia during ambulatory monitoring in this group of patients (88±14 versus 84±12 beats/min, p=NS).

Effects of Drug Treatment on Ischemic Threshold

1. Propranolol (group 3a). On placebo, the mean nonischemic heart rate was 74±8 beats/min, whereas the heart rate at onset of ischemia was 99±12 beats/min. During treatment, the nonischemic heart rate fell significantly to 62±6 beats/min (p<0.001 versus placebo), and the heart rate at onset of ischemia also fell, to 85±13 beats/min (p<0.001 versus placebo). The pattern of drug effects showed that ischemic events occurring at or above the median heart rate on placebo were almost completely eliminated by propranolol (Figure 6). Even though there was a reduction in ischemia overall, there was an increase in the number of events now occurring at lower heart rates compared with placebo (Figure 6).

2. Nitroglycerin (group 3b). Unlike propranolol, nitroglycerin therapy was associated with a rise in heart rate from 72±14 to 87±9 beats/min (p<0.05) and with only a modest reduction in the total number of ischemic events.12 Furthermore, nitroglycerin had an opposite effect on the distribution of ischemic events by heart rate, leading to fewer low heart rate events but to an increase in events at higher heart rates (Figure 7); this resulted in a small, but significant, rise in the mean heart rate at onset of ischemia from 94±15 on placebo to 103±15 beats/min on nitroglycerin (p<0.01).

The effects of treatment with propranolol and nitroglycerin on the distribution of ischemic events by

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<td>Resting heart rate (beats/min)</td>
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* p<0.05; † p<0.01.
heart rate are summarized in Table 3. Both treatments altered the distribution of ischemic events by heart rate but in opposite directions. Although propranolol markedly reduced the number of ischemic events by eliminating events at high heart rates, nitroglycerin reduced only events occurring at lower heart rates. The difference in the distribution of ischemic events by heart rate between the two treatments (propranolol and nitroglycerin) was highly significant \( p<0.0005 \).

**Discussion**

This study has shown that important increases in heart rate precede most ischemic events occurring in ambulant patients with coronary artery disease. However, these increases do not occur immediately before the onset of ischemia but between 5 and 30 minutes before each event. In addition, this study shows that the occurrence of ischemia at lower heart rates during daily life than during exercise testing may be explained, at least in part, by differences in the duration and intensity of exercise (or stress) because a longer duration of less-intense activity appears to be associated with a lower heart rate threshold for ischemia. Last, propranolol and nitroglycerin each had characteristic, but opposite, effects on transient myocardial ischemia occurring at high and at low heart rates. Whereas propranolol eliminates high heart rate ischemia while increasing low heart rate events, nitroglycerin decreases low heart rate events while increasing high heart rate ischemia.

Previous studies reported an increase, a decrease, and no change in heart rate before the onset of ischemia.\(^{2,4,9-11}\) Deanfield et al\(^4\) demonstrated that 77% of ischemic episodes were not accompanied by a rise in heart rate of more than 10 beats/min, whereas Chierchia et al\(^11\) demonstrated that 59% of episodes were accompanied by either no change in heart rate or a rise of less than 5 beats/min. Campbell et al\(^5\) demonstrated that 35% of ischemic episodes were associated with either no change or a decline in heart rate. The differences between our results and earlier studies relate to the timing of the observations and to the definition of nonischemic heart rate; in previous studies, heart rate at onset of 1 mm ST segment depression was compared with heart rate 1 minute\(^4,5\) and 15 minutes\(^11\) before ischemia. We may have introduced a bias in our analysis by calculating the baseline nonischemic heart rate from all time periods of the day when ischemia was absent, including during sleep, when heart rate is lower and ischemia occurs less frequently. However, analysis of the time course of the increase in heart rate from our data suggests that this does not account for the difference between nonischemic heart rate and heart rate at the onset of ischemia because heart rate 30 minutes before onset of ischemia is not significantly different from the entire nonischemic heart rate and

![FIGURE 5. Bar graphs of duration of increased heart rate for all episodes in which heart rate exceeded the lowest heart rate threshold for ischemia in that patient. When increased heart rate was accompanied by ischemia, the duration of the increased heart rate was greater (median, 35 minutes) than when heart rate increased without ischemia (median, 7.5 minutes, \( p<0.001 \)).](image-url)
because there was a significant increase in heart rate during the 30 minutes before ischemia.

We have no data relating to left ventricular function and cannot, therefore, comment on the temporal relation between wall motion abnormalities and ST depression in these patients. However, other studies in humans have suggested that left ventricular dysfunction precedes ST segment depression by only 15–60 seconds.\textsuperscript{21,23} Because an increase in heart rate was detectable 15 minutes before the onset of ST depression (Figure 4), it seems unlikely that this increase in heart rate is secondary to left ventricular dysfunction.

The absence of an increase in heart rate before ischemia during daily life, with the occurrence of ischemia at heart rates lower than during exercise testing, has led to the suggestion that many ischemic events are related to reduced coronary supply rather than to increased demand.\textsuperscript{4,11} We have no data relating to other determinants of myocardial supply and demand, such as coronary blood flow and left ventricular wall tension, and therefore we cannot extrapolate our data to answer questions relating to the causes of ischemia in ambulant patients. The increase in heart rate before the onset of ischemia could be causal at times. If it represents an increase in demand, it may represent increased activation of system(s), for example, sympathetic activity that could affect coronary blood supply as well. Nevertheless, our data demonstrate a strong association between increased heart rate and most ischemic events during daily life. The rise in heart rate, however, occurs over a prolonged period of time, usually 10–30 minutes before the onset of ischemia and is less than the rise in heart rate during standard Bruce protocol exercise testing. In contrast, several groups have demonstrated that most patients with frequent ischemia during Holter monitoring develop significant ST depression by stage 2 of the Bruce protocol, that is, within 6 minutes of starting to exercise.\textsuperscript{16,24}

We can speculate, therefore, that the ischemia-provoking stress during daily life is generally of longer duration and is less intense than the stress provided by a standard Bruce exercise protocol. In this study, subdivision of episodes of increased heart rate during ambulatory ECG monitoring demonstrated that the duration of heart rate increase was greater in those episodes that were accompanied by ischemia than in those that were not. Furthermore, a comparison of two exercise protocols demonstrated that a longer duration of less-severe exercise was associated with a reduction in the heart rate at onset of ischemia. These results support the hypothesis that a longer duration of less-strenuous activity during daily life can explain the appearance of ischemia at heart rates lower than those occurring during exercise testing.

Similar results were reported by Gerber et al.,\textsuperscript{25} who compared a Bruce protocol with a less-strenuous protocol incorporating a 20-minute submaximal steady-state period; they demonstrated that both the heart rate and blood pressure product and oxygen uptake were significantly lower at the onset of ischemia during the submaximal test. The physiological explanation for this is not clear. One possible explanation may be that increased cardiac demand is a function of both increased heart rate and time. The integral of heart rate and time could be achieved by altering both variables until myocardial reserves of oxygen and substrates are exhausted with sufficient accumulation of anaerobic products to result in ischemia.

This study shows that propranolol and nitroglycerin have opposite and characteristic effects on the distribution of ischemic events by heart rate. Propranolol diminishes ischemic events that occur at or higher than the mean heart rate at onset of ischemia during placebo. Interestingly, propranolol was associated with an increase in the number of events occurring at lower heart rates. One could speculate that demand-mediated ischemia is well treated by
propranolol, but the modest increase in coronary tone that occurs with this drug results in failure to eliminate, and even a small increase in, ischemic events occurring at lower heart rates (supply mediated). Alternatively, lower driving pressure at each coronary stenosis due to blood pressure reduction by propranolol may also explain these effects.

In contrast, nitroglycerin resulted in a decline in events occurring at lower heart rates. Again, one may speculate that the coronary vasodilator action of nitrates would benefit those ischemic events triggered by reduced supply but would not benefit demand-related events occurring at higher heart rates. These widely different drug effects suggest that the heart rate distribution of ischemic events may predict anti-anginal drug efficacy and may be helpful in tailoring drug therapy to the individual patient.

In conclusion, we have shown that significant increases in heart rate are strongly associated with myocardial ischemia during daily life and occur 5–30 minutes before the onset of ischemia. Because the development of ischemia is a function of both intensity of exercise and time, a modest rise in heart rate over a relatively long period of time may explain the reduced heart rate threshold for ischemia commonly described during daily life. Last, β-blockers and nitrates have opposite effects on ischemic events occurring at high and at low heart rates. Although controlled prospective studies are clearly required, it is possible that analysis of the heart rate distribution of ischemia in individual patients may assist in planning therapy.

References

KEY WORDS • ischemia • heart rate • ambulatory monitoring • propranolol • nitroglycerin
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