Role of Increases in Heart Rate in Determining the Occurrence and Frequency of Myocardial Ischemia During Daily Life in Patients With Stable Coronary Artery Disease

JULIO A. PANZA, MD, JEAN G. DIODATI, MD, FACC, TIMOTHY S. CALLAHAN, MS, STEPHEN E. EPSTEIN, MD, FACC, ARSHED A. QUYYUMI, MD

Bethesda, Maryland

Objectives. The goal of this study was to investigate the role of increases in heart rate in the development of ischemic episodes recorded during ambulatory electrocardiographic (ECG) monitoring in patients with stable coronary artery disease and to establish the importance of such increases in determining the frequency of ambulatory myocardial ischemia.

Background. The factors that determine the occurrence and frequency of episodes of myocardial ischemia that patients with stable coronary artery disease experience during daily life have not been clearly defined. In particular, the role of increases in heart rate in the development of myocardial ischemia is controversial.

Methods. To address these issues, 54 patients (42 men and 12 women, mean age 60.5 ± 8 years) with proved coronary artery disease who had ≥1 mm ST segment depression during exercise testing underwent an exercise treadmill test with use of the National Institutes of Health combined protocol and a 48-h period of ambulatory ECG monitoring. The exercise ischemic threshold was determined as the heart rate at the onset of ST segment depression during exercise testing.

Results. During monitoring, 48 (89%) of the 54 patients had at least one episode of ST segment depression (mean ± SD 6.6 ± 5 beats/min; the most significant increase [22.3 ± 10 beats/min] occurred during the 5-min period before the onset of the episode. An ischemic episode occurred 80% of the times the heart rate reached the exercise ischemic threshold. A strong correlation was observed between the number of times the exercise ischemic threshold was reached during monitoring and both the number and the duration of ischemic episodes (r = 0.90 and 0.71, respectively, p < 0.0001).

Conclusions. Increases in heart rate that exceed the exercise ischemic threshold are commonly observed before the onset of episodes of ambulatory myocardial ischemia in patients with stable coronary artery disease. Moreover, such increases constitute an important determinant of the frequency of myocardial ischemia during daily life. These findings may explain the variability observed in the number of ischemic episodes and may have important implications for the mechanisms that contribute to myocardial ischemia in daily life and for the clinical evaluation of patients with coronary artery disease.

(J Am Coll Cardiol 1992;20:1092-8)

Because of the potential clinical and prognostic implications, much attention has been directed to the study of episodes of myocardial ischemia that patients with stable coronary artery disease often experience during daily life (1-3). However, the mechanisms that participate in the triggering of these episodes and the determinants of their occurrence and frequency have not been clearly defined. In particular, the role of increases in heart rate in the development of ischemia is controversial because of the discrepant findings of previous studies. Some reports have shown that most episodes of ST segment depression during ambulatory electrocardiographic (ECG) monitoring are not preceded by significant increases in heart rate (4,5) and that the heart rate at which myocardial ischemia develops is clearly lower than the rate at the onset of ischemia during exercise testing (4-6). However, other studies, have yielded opposite results, showing that ischemic episodes during daily life are indeed often preceded by increases in heart rate (7-11).

We and others (6,8,12,13) have found a strong correlation between the results of exercise testing and ambulatory ECG monitoring in patients with stable coronary artery disease in that patients who develop ECG changes early during the exercise test, at a relatively low heart rate, have frequent episodes of myocardial ischemia during ambulatory monitoring, whereas patients with normal exercise test results or with ST segment depression that appears during the late stages of the test usually have no or few ischemic episodes. Although these findings indicate that the exercise ischemic threshold (the level of myocardial oxygen demand at which ischemia develops during exercise testing) is closely related...
to the presence and frequency of myocardial ischemia during daily life, some variability exists with regard to the number of ischemic episodes even in patients with a similar ischemic threshold during exercise testing. Also, significant variability has been reported in day to day measurements of myocardial ischemia (14,15). Such variability in the number of ischemic episodes could be explained by the frequency with which increases in heart rate exceed the ischemic threshold during monitoring in each patient.

The present study was therefore undertaken with the following objectives: 1) to investigate the role of increases in heart rate in the development of episodes of myocardial ischemia in patients with stable coronary artery disease, and 2) to establish the importance of such increases in heart rate as determinants of the frequency of myocardial ischemia during daily life.

**Methods**

Study patients. Fifty-four consecutive patients with stable coronary artery disease who had a positive treadmill exercise test result (that is, planar or downsloping ST segment depression ≥1 mm at 0.08 s after the J point) were included in this study, which was approved by the National Institutes of Health Investigational Review Board. There were 42 men and 12 women; the mean age was 60.5 ± 8 years (range 42 to 75). All patients had undergone cardiac catheterization as part of their evaluation for suspected coronary artery disease, chest pain syndrome or previous myocardial infarction. Coronary angiograms were interpreted by an independent reader; a significant stenosis was considered as ≥70% narrowing in the internal diameter of at least one major coronary artery. Twenty-three patients (42%) had one-vessel disease, 21 (39%) had two-vessel disease and the remaining 10 patients (19%) had involvement of all three major coronary vessels. Thirty-five patients were asymptomatic and 19 had stable symptoms. None had had a myocardial infarction in the 3 months before the study. Thirty-two of the 54 study patients had also participated in a previous study designed to investigate the importance of the exercise protocol in determining the relation between exercise testing and ambulatory ECG monitoring (13). Patients with left bundle branch block, ECG signs of left ventricular hypertrophy or strain, as well as patients taking digitalis or diuretic drugs, were not included in the study.

After informed consent was obtained, patients underwent a treadmill exercise test followed by one period of ambulatory ECG monitoring. All studies were performed after withdrawal of antianginal medications for at least 48 h, although this interval was longer in patients taking long-acting medications. During ambulatory monitoring, patients were allowed to take sublingual nitroglycerin for chest pain but not prophylactically.

Exercise testing. Exercise treadmill tests were performed with use of the National Institutes of Health (NIH) combined protocol (13,16). This exercise protocol employs slow increments in work load, allowing accurate estimation of the ischemic threshold that closely correlates with the results of ambulatory ECG monitoring (13). The NIH combined protocol has also proved useful for the serial noninvasive evaluation of patients with coronary artery disease (16).

Patients exercised until one of the following developed: severe chest pain, ST segment depression ≥4 mm, ≥20 mm Hg decrease in systolic blood pressure, ventricular tachycardia, extreme fatigue or shortness of breath. Twelve-lead ECGs were obtained at rest, at every minute during exercise and at peak exercise. On the ECG, lead aVR was replaced by lead CM₅. Test results were considered positive for ischemia when planar or downsloping ST segment depression ≥1 mm at 0.08 s after the J point, was observed during exercise.

For the purpose of correlation with the results of ambulatory ECG monitoring, the exercise ischemic threshold was determined as the heart rate at the onset of ST segment depression. We have previously shown (13) that this measurement correlates significantly with the number and duration of ischemic episodes during ambulatory ECG monitoring when it is obtained with an exercise protocol, such as the NIH combined protocol, that produces slow increases in work load. Although the time of exercise at the onset of ST segment depression correlates significantly with the number and duration of ischemic episodes during monitoring (13), it is not possible to obtain a similar measurement from analysis of the ambulatory ECG monitoring tracings. For this reason, only the heart rate at the onset of ST segment depression (which can be measured during both exercise testing and ambulatory monitoring) was utilized in this study as an expression of the ischemic threshold.

For the overall patient group, the onset of ST segment depression during both exercise testing and ambulatory ECG monitoring was defined as the earliest ECG manifestation of repolarization changes characteristic of myocardial ischemia that preceded the development of more pronounced and definite changes in the ST segment. This early manifestation of repolarization abnormalities was usually recognized when the ST segment shift was 0.5 mm, although in some patients it was possible to identify ECG tracings showing even more minor changes (that is, ST segment depression of 0.25 mm). Therefore, to ensure comparability of the readings, the ECG tracings from ambulatory monitoring and exercise testing were matched in lead CM₅ in retrospect for each individual patient, so that the extent of repolarization changes identified as the onset of ST segment depression was similar for both tests. Lead CM₅ was chosen for this purpose because it consistently allowed earlier detection of ECG changes during both exercise testing and ambulatory monitoring than did modified lead II.

Ambulatory electrocardiographic monitoring. Each patient underwent a 48-h period of ambulatory ECG monitoring with lead CM₅ and modified lead II (8). Patients were instructed to carry out their normal daily activities and to keep a detailed diary of their activities, symptoms and
consumption of sublingual nitroglycerin. Tapes were analyzed by an independent reader at 60 to 120 times normal speed utilizing a Del Mar Avionics model 750A system. Printouts at a paper speed of 25 mm/s were obtained before, during and after any change in the ST segment level. An ischemic episode was defined as ≥1 mm ST segment depression, at 0.08 s after the J point, lasting for ≥1 min. Return of ST segment level to baseline for ≥3 min was required between two episodes. The magnitude of myocardial ischemia during daily life was assessed as 1) the number, and 2) the total duration of ischemic episodes during the period of monitoring. The duration of each episode was determined from the lead that showed the more prolonged ECG changes (lead CM<sub>3</sub> in the vast majority of cases).

For each patient the heart rate and ST segment trends were analyzed to determine 1) the number of times during the period of ambulatory ECG monitoring that the heart rate reached the ischemic threshold measured during exercise testing; 2) the duration of each instance of increase in heart rate, measured as the time during which the heart rate remained above the exercise ischemic threshold; and 3) the occurrence (or nonoccurrence) of an ischemic episode when the heart rate reached the exercise ischemic threshold. The number of times the heart rate reached the exercise ischemic threshold and the number of ischemic episodes during monitoring were also analyzed separately for each of the two 24-h periods within the 48-h monitoring period.

For each ischemic episode, the heart rate at the onset of ST segment depression was determined. In addition, the heart rate at 15 and 5 min before the onset of ST segment changes and at the development of 1 mm of ST segment depression was also determined. In patients with more than one ischemic episode during monitoring, the values for heart rate at the onset of ST segment depression for each episode were averaged for the purpose of correlation with the heart rate at the onset of ST segment change during exercise testing.

Statistical analysis. Mean values during exercise testing and ambulatory ECG monitoring were compared by using the paired t test. Relation between different variables were assessed by means of Pearson's correlation coefficient. Changes in heart rate surrounding an ischemic episode were analyzed by analysis of variance combined with multiple comparisons utilizing the Newman-Keuls procedure. A p value <0.05 was considered significant. All data are expressed as mean value ± SD.

Results

Exercise testing. The mean exercise duration for the 54 study patients was 13.5 ± 4 min and the maximal work load achieved was 6.1 ± 2 METS. All patients had ≥1 mm ST segment depression at peak exercise. Twenty-six patients developed chest pain during exercise. The reason for terminating the test was chest pain in 21 patients, significant ST segment depression (≥4 mm) in 5 and fatigue or breathlessness in 28. No patient had ventricular arrhythmias or a significant (>20 mm Hg) decrease in systolic blood pressure. The exercise ischemic threshold (heart rate at the onset of ST segment depression) in the 54 study patients ranged from 70 to 146 beats/min (mean 102 ± 16).

Ambulatory electrocardiographic monitoring. During the 2,554 h that were suitable for ST segment analysis, 48 (89%) of the 54 study patients had at least one episode of ST segment depression. This relatively high prevalence of myocardial ischemia during ECG monitoring was probably due to our limitation of the study group to patients with inducible ischemia during exercise testing who had discontinued all anti-ischemic medications before study. A total of 359 ischemic episodes were recorded, of which 315 (87%) were silent. The average number of episodes/patient during the 48 h of recording was 6.6 ± 5 (range 0 to 22). The total duration of ischemia was 10,278 min (86% silent) with a mean of 190 min/patient (range 0 to 956). Although the ischemic episodes were identified in lead CM<sub>3</sub> in all study patients, in 10 patients modified lead II failed to reveal concomitant ST segment depression ≥1 mm.

The heart rate at the onset of ischemic episodes ranged from 66 to 138 beats/min. Ischemic episodes were associated with significant increases in heart rate (p < 0.0001 by analysis of variance). A minor but statistically significant increase in heart rate (3.5 ± 4 beats/min) was observed between 15 and 5 min before the onset of ST segment depression; the most significant increase (22.3 ± 10 beats/min or 28.2 ± 17%) occurred during the 5 min before the onset of the episode; a further increase (mean 4.2 ± 5 beats/min) was observed between the onset and the development of 1-mm ST segment depression (Fig. 1). Most ischemic episodes (320 or 89%) were preceded by an increase in heart rate ≥10 beats/min.

Forty-three patients had two or more ischemic episodes; in some of these patients, substantial variability was found in the heart rate at the onset of ST segment depression during monitoring. The maximal difference within individual patients was 18.1 ± 11 beats/min (range 0 to 49).

Relation between ambulatory myocardial ischemia and the exercise ischemic threshold. The exercise ischemic threshold measured during treadmill exercise testing had a significant inverse correlation with both the number and the duration of ischemic episodes during ambulatory ECG monitoring (Fig. 2). Thus, patients with a lower exercise ischemic threshold (relatively low heart rate at the onset of ST segment depression during exercise testing) had more ischemic episodes and a longer duration of ischemia during ambulatory monitoring than did patients with higher exercise ischemic threshold.

For the 48 patients who developed ischemic episodes during ambulatory ECG monitoring, the heart rate at the onset of ST segment depression was similar during monitoring and exercise testing (98.1 ± 10 and 99.9 ± 12 beats/min, respectively, p = NS) (Fig. 1). Moreover, a close correlation was observed between the heart rate at the onset of ST segment depression during exercise testing and during
Figure 1. Changes in heart rate before and during 359 ischemic episodes recorded during ambulatory electrocardiographic (ECG) monitoring in 48 patients with stable coronary artery disease. For this analysis, each of the 359 ischemic episodes was assessed individually. The most significant increase in heart rate (22.3 ± 10 beats/min) occurred during the 5 min before the onset of ST segment depression (ST \$). No significant difference was observed between the ischemic threshold measured during exercise testing (mean ± SD, represented by the shaded area) and the onset of ST segment depression during ambulatory ECG monitoring. Differences are significant at a level of p < 0.05 (*) or p = 0.01 (**) by multiple comparisons procedure.

Figure 2. Correlation between the exercise ischemic threshold, measured as the heart rate at the onset of ST segment depression (ST \$) during exercise testing, and the number and duration of episodes of myocardial ischemia during ambulatory electrocardiographic monitoring in 54 patients with stable coronary artery disease.

Discussion

Although patients with stable coronary artery disease often have episodes of myocardial ischemia during daily life (1-3), the factors that determine the frequency of their occurrence are still controversial. The debate concerning this subject centers largely on the role that increases in heart rate play in the development of myocardial ischemia (4-11).

Increases in heart rate and myocardial ischemia. Our findings demonstrate that increases in heart rate are commonly observed before the onset of episodes of myocardial ischemia during daily life in patients with stable coronary artery disease. Thus, about 90% of the ischemic episodes recorded during ambulatory ECG monitoring in our study patients were preceded by significant increases in heart rate (≥10 beats/min). These results are in agreement with those of recent reports from two independent laboratories (10,11) showing that significant increases in heart rate usually precede ischemic episodes during daily life. However, in contrast to the study of McLenachan et al. (11), in our patients the greatest increase in heart rate occurred in the 5 min before the onset of repolarization changes. Because of the
intrinsic delay between the actual onset of myocardial ischemia and the appearance of ECG changes, it is possible that this increase in heart rate was partly a consequence of myocardial ischemia that developed before the first ST segment changes were detected. However, the contribution of this mechanism to the total increase in heart rate preceding the onset of ST segment depression is probably minimal, because the increases in heart rate started even earlier than 5 min before the appearance of repolarization changes, as also demonstrated by McLenachan et al. (11).

Our findings indicate that increases in heart rate during daily life often precipitate myocardial ischemia when they exceed the exercise ischemic threshold (the level of myocardial oxygen demand at which ischemia develops during exercise testing). Thus, during ambulatory ECG monitoring an ischemic episode occurred 80% of the times that the heart rate increased to the level measured at the onset of myocardial ischemia during exercise testing. The duration of increase in heart rate seems to be important in determining the occurrence of ischemia, because the periods of heart rate increase associated with ischemia were significantly longer than those in which ischemia did not develop, as in previous studies (11).

Our results also indicate that increases in heart rate constitute an important determinant of the frequency of myocardial ischemia during daily life in patients with stable coronary artery disease. This observation is based on the strong correlation between the magnitude of myocardial ischemia (number and duration of ischemic episodes) and the frequency with which the exercise ischemic threshold was reached during the period of monitoring. This finding may explain, at least in part, the variability observed in the number of ischemic episodes, even among patients with a similar exercise ischemic threshold. Furthermore, the observation that, within an individual patient, the frequency with which the heart rate reached the exercise ischemic threshold was higher on the day with more ischemic episodes suggests that this is an important factor in the day to day variability observed in the frequency of myocardial ischemia in coronary artery disease (14,15).

Mechanisms of myocardial ischemia during daily life. Our findings suggest that increases in myocardial oxygen demand, represented by increases in heart rate, constitute an important mechanism of production of transient ischemic episodes during daily life in patients with stable coronary artery disease. Other determinants of myocardial oxygen demand, such as blood pressure and contractility, were not measured in our study. Previous investigations that included analysis of ambulatory blood pressure have shown that significant increases in both heart rate and blood pressure often precede the onset of ischemic episodes (8,10), further supporting the role of increased myocardial oxygen demand in myocardial ischemia during daily life. In addition, it has been shown that surges in blood pressure without major changes in heart rate usually precede the development of myocardial ischemia during mental stress (17).

However, certain of our findings also emphasize the role of dynamic changes in coronary blood flow in determining myocardial ischemia. 1) About 10% of episodes were not preceded by a significant increase in heart rate; 2) 15% of episodes occurred at a heart rate considerably below (≥10 beats/min) the exercise ischemic threshold measured during exercise testing; 3) no ST segment depression was observed 20% of the times that the exercise ischemic threshold was reached during ambulatory ECG monitoring; and 4) the heart rate at the onset of ST segment depression during monitoring showed a great degree of variability within individual patients. All these observations probably reflect the pathophysiologic significance of dynamic changes in the coronary vasculature during daily life as a consequence of variations in the autonomic tone (18) or other mechanisms that contribute to the development of myocardial ischemia. These changes in coronary blood supply may act either by modifying the level of myocardial oxygen demand at which ischemia occurs (19–21) or by producing myocardial ischemia even without a prior increase in myocardial demand.

Implications. Our results may have important clinical implications: 1) Because the majority of ischemic episodes are preceded by increases in heart rate that achieve the exercise ischemic threshold, a reduction in these episodes would be best obtained with therapy directed toward both prevention of increases in heart rate, as supported by studies showing a beneficial effect of beta-adrenergic blocking agents (22–24), and elevation of the exercise ischemic threshold, as indicated by the reduction in myocardial ischemia after revascularization procedures (25–27). 2) Because
Figure 4. Heart rate and ST segment trends obtained during ambulatory electrocardiographic (ECG) monitoring in two patients with stable coronary artery disease. The ischemic threshold measured at exercise testing has been traced on the heart rate trend. A, A 50-year-old woman with single-vessel coronary artery disease and a relatively high exercise ischemic threshold (122 beats/min). During ambulatory ECG monitoring, several increases in heart rate were observed, but ST segment depression developed only when the heart rate increased above the exercise ischemic threshold. B, A 65-year-old man with three-vessel coronary artery disease and a relatively low exercise ischemic threshold (85 beats/min). During ambulatory ECG monitoring, an ischemic episode was observed each time the heart rate increase reached the exercise ischemic threshold.

Figure 5. Correlation between the number of times the exercise ischemic threshold was reached during the period of ambulatory electrocardiographic monitoring and the number and duration of ischemic episodes in 54 patients with stable coronary artery disease.

Limitations of the study. Certain aspects of the design of our study must be considered in interpreting our results. 1) Because our study group included only patients with angiographically proved coronary artery disease and a symptomatically stable clinical course, our findings may not be applicable to other subsets of patients with ischemic heart...
disease, such as patients with unstable angina or a recent myocardial infarction or those without significant narrowing of the epicardial vessels. Also, because our study included only patients whose exercise test result was positive for ischemia and who were studied when they were not receiving antianginal medications, our findings may not be applicable to the entire cohort of patients with stable coronary artery disease. 2) Because the relation between the results of exercise testing and ambulatory ECG monitoring is dependent on the exercise protocol (13), the magnitude of myocardial ischemia during daily life may not be predicted by the ischemic threshold measured during exercise testing with use of protocols with faster increments in work load than those we used. 3) Because we did not obtain blood pressure recordings during daily activities, we cannot determine the role that blood pressure surges may have played in determining the occurrence and frequency of myocardial ischemia during daily life in our patients. 4) The episodes of increased heart rate observed during ambulatory ECG monitoring probably represent the physical and mental activities that patients perform as part of their daily routine. Although these activities would theoretically be reflected in the diaries that patients are instructed to keep during the period of monitoring, such diaries are generally insufficient to permit a detailed and reliable assessment of all activities performed during the day. For this reason, we cannot ascertain to what extent the different number of ischemic episodes in patients with a similar exercise ischemic threshold or the day to day variability within individual patients can be explained by different frequencies with which physical and mental activities are performed during the monitoring period.

Conclusions. Our study demonstrates that increases in heart rate that reach the ischemic threshold measured during exercise testing usually precede the development of myocardial ischemia during daily life in patients with stable coronary artery disease. Moreover, these increases in heart rate importantly determine the frequency of myocardial ischemia in these patients. These findings participate in our understanding of the mechanisms that contribute to the production of myocardial ischemia during daily life and have implications for the clinical evaluation and treatment of patients with stable coronary artery disease.

References