Features of the exercise test that reflect the activity of ischemic heart disease out of hospital

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ABSTRACT To better understand the relationship between the transient myocardial ischemia seen during an exercise test and ischemic activity out of hospital, 39 patients with well-documented coronary artery disease underwent standard treadmill exercise testing (Bruce protocol) and 24 to 48 hr of continuous ambulatory electrocardiographic monitoring during normal daily activities. A total of 245 episodes of transient ischemia were recorded in 21 of 32 patients with positive exercise electrocardiograms (group I), whereas seven patients with negative test results (group II) had no episodes of transient ischemia, during monitoring out of hospital (p < .01). Certain measures in the exercise test were related to the severity of ischemia out of hospital: there were more episodes and a greater total duration of transient ischemia per 24 hr of ambulatory monitoring in patients who developed ischemic electrocardiographic changes before 6 min of exercise (p ≤ .021) or at a heart rate of less than 150 beats/min (p = .005) and in those in whom these ST segment changes persisted for more than 5 min after exercise (p ≤ .016). In contrast, there was no relationship between transient ischemia out of hospital and the commonly quoted exercise variables: chest pain, total exercise duration, and the maximum levels of heart rate, systolic blood pressure, and double product. Thus, patients with coronary artery disease and negative exercise electrocardiograms are most unlikely to experience active ischemia during normal daily life. However, certain features of the positive exercise test, namely the exercise duration at onset of significant ST depression, the heart rate at this threshold point, and the persistence after exercise of these ischemic changes, are all related to the level of this disease activity during daily life. This may help to assess risk and explain why the early positive exercise test is an adverse sign for coronary events.


EXERCISE TESTING is widely used in the hospital as a noninvasive means of assessing patients with suspected or established coronary artery disease. The evolution of characteristic ST segment changes is used as an indicator of transient myocardial ischemia, especially when accompanied by chest pain. Moreover, such changes and their severity are believed by some authorities to be of value in predicting prognosis and the severity of disease.

Recent studies using ambulatory monitoring of ST segment changes as a marker of ischemia in patients with angina, positive exercise test results, and coronary artery disease have, however, revealed that the majority of patients studied had frequent and usually asymptomatic episodes of ST depression. Many of these episodes occurred at rest or during light activities, with little or no increase in heart rate.

The characteristics of ischemic changes occurring during normal daily activities out of hospital thus appear to differ in several respects from those induced by exercise testing in hospital. Our aims, therefore, were (1) to determine the relationship between ischemia induced in hospital and that occurring out of hospital and (2) to determine if there are any specific features of the routinely used standard treadmill exercise test that reflect the activity of ischemic heart disease out of hospital.

Methods

Two groups of subjects were selected from those seen as outpatients or undergoing investigation between December 1984 and February 1986.

Group 1 comprised 32 patients, 29 men and three women.
Their mean age was 56.3 (range 34 to 75) years; all had exercise stress tests positive for ischemia (ST segment depression ≥0.1 mV, persisting 0.08 sec beyond the J point for 3 consecutive beats in any lead) and at least one of the following additional criteria for ischemic heart disease: (1) typical symptoms of angina pectoris, (2) documentation of previous acute myocardial infarction by at least two of the following criteria: characteristic history or enzyme or electrocardiographic changes, and (3) angiographic documentation of significant obstructive coronary artery disease, defined as 70% or greater stenosis of one or more coronary arteries.

Group II comprised seven male subjects, mean age 49.9 (range 37 to 60) years, all of whom had previous exercise test results consistently negative for ischemia but who had evidence of ischemic heart disease by documentation of myocardial infarction as above. In addition five of the seven had undergone angiography with demonstration of significant coronary artery disease, also as defined above.

Patients with atrial fibrillation, electrocardiographic conduction defects, marked left ventricular hypertrophy, significant valvular disease, or taking digoxin were not included. All patients gave informed consent.

**Exercise stress testing.** Each patient performed a treadmill exercise test by the standard Bruce protocol. Blood pressures were measured with a cuff sphygmomanometer and 12-lead electrocardiograms were recorded in patients in the supine and erect positions before starting exercise. The electrocardiogram was monitored continuously usually via leads II, V2, and V5. Twelve-lead electrocardiograms were recorded at minute intervals, at the onset of ST segment depression, at peak exercise, and at regular intervals after exercise, with the patient supine, until any changes had resolved or for a minimum of 6 min. Blood pressures were recorded at the end of each 3 min exercise stage, at peak exercise, and at intervals during postexercise recovery along with the electrocardiogram. The patients were instructed to exercise until limited by symptoms of fatigue or increasing chest pain. In addition exercise was stopped if ST depression of 4 mm or more developed, there was a sustained fall in systolic blood pressure of 20 mm Hg or more, significant ventricular arrhythmias developed, or, as in one case, when the maximum predicted heart rate was achieved after prolonged exercise.

In each patient the following exercise parameters based on data from previous studies1-4, 16-22 were recorded: (1) the presence or absence of typical ischemic chest pain, (2) the time of onset of ST segment depression (≥0.1 mV), (3) its maximum depth, and (4) its persistence after exercise, (5) the heart rate at the onset of ST segment depression of 0.1 mV, (6) the maximal rate achieved, (7) the increments from the resting level to these points, (8) the blood pressure at peak exercise, (9) the change in blood pressure from rest to this point, (10) the double product of heart rate and systolic blood pressure at peak exercise, and finally (11) the maximum duration of exercise.

**Ambulatory Holter monitoring.** All patients underwent one or more periods of continuous 24 hr electrocardiographic monitoring within 1 day (median) of the exercise test (range 1 day to 15 weeks). The recordings were made with a calibrated Oxford Medilog 2 frequency-modulated recorder with two bipolar leads attached to exploring electrodes, usually at the standard V5 and modified inferior positions. This scheme was occasionally altered on the basis of exercise electrocardiographic results to ensure that the most positive leads were monitored. The recorders were calibrated with standard 1 mV signals and patients were then instructed to carry on with their normal daily activities, other than bathing, and record any symptoms in a structured diary while wearing the devices.

The tape recordings were visually analyzed at 60 or 120 times real time with the use of an Oxford Medilog MA 20 scanner. Calibration and baseline traces were printed out as was each episode of ST segment depression that fulfilled the following criteria: (1) planar or downsloping ST depression of 0.1 mV or more persisting 0.08 sec beyond the J point, and (2) changes present in consecutive beats for a minimum of 30 sec. The duration of an episode was defined as the total number of minutes with 0.1 mV or more ST depression. Separation of one episode from the next required the electrocardiogram to return to baseline for at least 3 min. All the tapes were analyzed independently by two experienced readers. The results were then reviewed together and only those episodes on which there was complete agreement were included in the final analysis. The following features were noted for each episode of ST segment depression: (1) the times of onset and offset, (2) the duration in minutes, (3) the heart rate in the minute preceding the episode, (4) the heart rate at its onset, and (5) the peak rate attained during the episode.

**Therapy.** Thirty-two of the 39 patients studied exercised and were monitored off any regular specific drug therapy except for nitroglycerin as required. For the remaining seven patients medication was not discontinued but was consistent for the exercise test and monitoring periods.

**Data analysis.** The exercise test data are expressed as mean ± SD for the various parameters. The summary data from the ambulatory monitoring studies are expressed as median values with ranges in parentheses (because of their nonparametric distribution). Various exercise parameters were selected, based on previous studies,1-8, 14-22 and were plotted against the frequency and duration of transient ischemia recorded for each patient during ambulatory monitoring. The relationship between the exercise variables and the findings on ambulatory monitoring was further examined by the Wilcoxon rank-sum test for unpaired data. In addition the chi-square test and unpaired t test were used to examine differences between proportions and means, respectively, and the Kruskal-Wallis test23 was used for multiple group nonparametric analysis when appropriate.

**Results**

**Patient characteristics**

**Group I.** The 32 patients studied were classified symptomatically by the New York Heart Association (NYHA) criteria.24 Thus, 15 (47%) were in class I, 12 (37%) were in class II, and five (16%) were in class III. Angiographic data were available for 28 (88%) patients and 10 (36%) of these had single-vessel, 11 (39%) had double-vessel, and seven (25%) had triple-vessel disease or worse (including two patients with left main disease). Four patients had undergone previous coronary bypass surgery but all had experienced recurrent symptoms and had positive exercise test results. The clinical details are presented in table 1.

**Group II.** All seven patients were in NYHA class I. Five patients (71%) had undergone angiography and three (60%) of these had single-vessel, one (20%) had double-vessel, and one (20%) had triple-vessel disease. These details are also summarized in table 1.

**Exercise testing.** All the exercise tests were successfully completed without any complications.

**Group I.** All the patients developed at least 0.1 mV
ST segment depression and 19 developed chest pain. Exercise was stopped because of increasing chest pain in 15 patients, a combination of fatigue, dyspnea, and chest pain in three, fatigue and dyspnea alone in nine, marked ST depression in two, hypotension in two, and achievement of the maximum predicted heart rate in one. ST segment depression of 0.1 mV developed at 3.8 $\pm$ 2.6 min. The heart rate at this threshold point was 125 $\pm$ 21 beats/min after an increase of 47 $\pm$ 20 beats/min from the resting level. Patients exercised for a total of 5.9 $\pm$ 2.9 min and the maximum level of ST segment depression was 0.23 $\pm$ 0.11 mV. The maximum heart rate was 134 $\pm$ 21 beats/min, an increase from rest of 55 $\pm$ 23 beats/min. Peak exercise systolic blood pressure was accurately recorded in 31 patients and was 155 $\pm$ 29 mm Hg, which represented a change from rest of 18 $\pm$ 26 mm Hg. The double product of heart rate and systolic blood pressure at peak exercise in these patients was 21.0 $\pm$ 6.5 $\times$ 10^3 beats/min $\times$ mm Hg. After cessation of exercise, ST segment depression persisted for 9.9 $\pm$ 6.8 min in the 28 patients for whom these data were accurately recorded.

**Group II.** None of these patients developed ST segment depression or chest pain. All exercised to a symptom-limited end point and stopped because of fatigue with or without dyspnea. The mean duration of exercise was 9.0 $\pm$ 3.1 min; the maximum heart rate achieved was 154 $\pm$ 21 beats/min and the maximum systolic blood pressure was 166 $\pm$ 21 mm Hg, which represented changes from rest of 68 $\pm$ 13 beats/min and 47 $\pm$ 12 mm Hg, respectively. The peak double product was 25.6 $\pm$ 5.4 $\times$ 10^3 beats/min $\times$ mm Hg.

**Ambulatory monitoring**

**Group I.** The study population underwent a total of 1380 hr of ambulatory monitoring during normal daily activity out of hospital. Altogether 245 episodes of ST segment depression were recorded during this period, with a total duration of 2275 min. The episodes ranged in duration from 1 to 114 min (median = 5 min) and 183 (75%) were 10 min long or less. Chest pain was infrequent and 230 (94%) episodes were asymptomatic.

An increase in heart rate ranging from 1 to 50 beats/min (median = 8 beats/min) preceded 147 (60%) of the 245 episodes, but there was no change in heart rate between the minute before and the onset of significant ST depression in 39 (16%) episodes and an actual decrease in heart rate ranging from 1 to 20 beats/min (median = 6 beats/min) preceded 50 (24%) episodes.

The number of episodes and total duration of transient ischemia per patient per 24 hr ranged from 0 to 14 (median = 2.75) and 0 to 171.5 min (median = 22.3 min), respectively. Eleven of the 32 patients in group I had no episodes of transient ischemia during a total of 456 hr of ambulatory monitoring.

**Group II.** No episodes of ST segment depression

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**TABLE 1**

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MI = myocardial infarction; AMI = anterior MI; PMI = posterior MI; IMI = inferior Q wave infarction; SEMI = non-Q wave infarction; LMI = lateral MI.

*Exploded Patients with previous coronary bypass surgery.*
were recorded during a total of 312 hr of ambulatory monitoring during normal daily activities.

Relationship of findings on ambulatory monitoring to exercise test results. The results of the ambulatory monitoring standardized as above to number of episodes and total duration of ischemic ST segment depression per 24 hr per patient were related to selected exercise variables for each patient. There was no relationship apparent between ischemia during ambulatory monitoring and the following exercise parameters, irrespective of the development of ischemic changes during exercise testing: (1) the presence or absence of chest pain, (2) total exercise duration (figure 1), (3) maximum heart rate achieved, expressed as an absolute term or as a percentage of predicted maximum, (4) the increment in heart rate from rest to the maximum rate achieved, (5) the maximum systolic blood pressure attained, (6) the change in systolic pressure from the resting level, and finally (7) the double product of heart rate and systolic blood pressure at peak exercise.

However, the development of ischemic ST segment depression during exercise testing was related to transient ischemia during ambulatory monitoring out of hospital. Thus, 21 of the 32 patients in group I had one or more episodes of significant ST segment depression per 24 hr of monitoring, whereas none were detected in the seven patients in group II ($\chi^2 = 7.49, p < .01$).

In addition, in the group I patients three exercise parameters associated with the onset and duration of ST segment depression were related to the frequency and duration of ischemic episodes during ambulatory monitoring. (1) Exercise time to significant ST segment depression (0.1 mV). Thus, the 25 patients who developed significant ST depression before 6 min (end of stage II) of exercise had a median of 4.5 episodes of transient ischemia (range 0 to 14), and a median total duration of ischemia of 30 min (range 0 to 171.5) per 24 hr of monitoring. In contrast, the seven patients who only developed significant ST depression after 6 min or more of exercise had a median of 0 episodes (range 0 to 2) ($p = .005$) and median total duration of 0 min (range 0 to 33) ($p = .021$) of transient ischemia per 24 hr of monitoring (figure 2). (2) Heart rate at the onset of significant ST segment depression during exercise. Twenty-seven patients developed significant ST segment depression at a heart rate of less than 150

**FIGURE 1.** Relationship of total exercise duration in minutes during the Bruce protocol exercise test (ETT) to ischemic activity out of hospital as detected by ambulatory monitoring, expressed as number of ischemic episodes per 24 hr (left) and total duration of ischemia in minutes per 24 hr (right). No significant relationship was apparent. * = group I patients. $\triangle$ = group II patients.
beats/min during exercise testing. They had a median of 3.5 episodes (range 0 to 14) and a median total duration of 30 min (range 0 to 171.5) of transient ischemia per 24 hr of ambulatory monitoring, whereas the five patients who developed significant ST segment depression during exercise only at heart rates of 150 beats/min or more had no episodes of transient ischemia at all (p = .005 for both frequency and duration). (3) Persistence of significant ST depression after exercise. These data were accurately recorded in 28 of the 32 patients studied. In the postexercise recovery period significant ST segment depression persisted for more than 5 min in 22 of these patients who had a median of 4.0 episodes (range 0 to 14) and a median total duration of 28 min (range 0 to 171.5) of transient ischemia per 24 hr of monitoring. In contrast, the six patients in whom exercise-induced ST segment depression had resolved by 5 min or less of recovery had a median of 0 episodes (range 0 to 3) (p = .016) and a median total duration of 0 min (range 0 to 5.5) (p = .009) of transient ischemia per 24 hr of ambulatory monitoring.

There was no relationship evident between the change in heart rate from rest to the onset of significant ST segment depression or the maximum depth of ST segment depression during exercise and transient ischemia during ambulatory monitoring.

Significance of chest pain. Chest pain developed during exercise testing in 19 patients, all of whom were in group I. Twelve of these had episodes of transient ischemia on ambulatory monitoring. However, nine of the 20 patients with no chest pain on exercise also had similar transient ischemia and the difference was not significant.

Interestingly though, 15 (11%) of the 141 episodes recorded during ambulatory monitoring in the 12 patients who had chest pain on exercise testing were symptomatic, whereas all of the 104 episodes that occurred in the nine patients who did not develop chest pain on exercise testing were asymptomatic ($\chi^2 = 11.78$, p < .001).

Heart rate threshold for ischemia. In the group of 21 patients who exhibited ischemic ST segment changes both during the exercise test and during ambulatory
monitoring the mean heart rates at onset of ischemia were 121 ± 17 vs 98 ± 18 beats/min, respectively (p < .001).

**Relationship of findings on ambulatory monitoring to angiographic severity of disease.** Coronary angiographic results were available for 33 of the 39 patients studied. However, four had undergone previous coronary bypass surgery and were excluded from this analysis. Of the remaining 29 patients, 13 had single-vessel, 11 had double-vessel, and five had triple-vessel disease or worse.

As the number of vessels with significant disease increased, the frequency and total duration of ischemia recorded during ambulatory monitoring also increased, but the range in each angiographic category was considerable and the differences were not significant.

**Discussion**

This study has shown that in patients with ischemic heart disease the standard treadmill exercise test, performed in hospital, can give some indication of the level of disease activity out of hospital, as recorded by continuous ambulatory monitoring.

Patients without electrocardiographic evidence of induced ischemia during symptom-limited exercise testing did not appear to have any episodes of transient ischemia during usual activities; such episodes were only detected in patients with “positive” tests and certain features of the exercise test seemed to be useful indicators of this disease activity out of hospital. Thus, patients who developed ischemic ST segment changes before completing 6 min of exercise or at heart rates of less than 150 beats/min experienced significantly more episodes of transient ischemia of greater total duration per 24 hr of ambulatory monitoring than did those who only experienced ischemia after 6 min or more of exercise or at a heart rate of 150 beats/min or greater, respectively. Similarly, transient ischemic episodes during ambulatory monitoring were more frequent and had a greater total duration in patients in whom ischemic ST segment changes persisted for longer than 5 min after exercise than in the group in which these changes had resolved by 5 min or less. None of the other exercise variables examined were related to the frequency or duration of transient ischemia recorded out of hospital. Also, the severity of coronary artery disease as determined by angiography was an unreliable guide to ischemia during daily life.

Exercise-induced chest pain has long been recognized as a symptom of ischemia, but it proved to be an unreliable indicator of ischemic activity out of hospital and it has become increasingly recognized that many patients with ischemic heart disease may be totally asymptomatic.

Exercise testing has proved to be useful in giving some indication of the severity of coronary artery disease and in risk stratification in populations with confirmed or a high probability of disease. There remains, however, some controversy as to which exercise variables are of greatest value. The electrocardiographic signs of ischemia have been shown in some studies to be useful in assessing prognosis and the severity of coronary disease, whereas in other studies little value has been accorded to their occurrence and greater emphasis has been placed on the hemodynamic consequences of ischemia, owing to the deleterious effects on left ventricular function.

While symptom-limited or maximal exercise testing has proven to be useful in assessing ischemic heart disease, it represents only one form of stress, and few people routinely exercise to their maximum capacity. Furthermore, recent studies with ambulatory monitoring of ischemic ST segment changes in well-characterized patients with ischemic heart disease have shown that most episodes of ischemia that occur during normal daily life do so at relatively low heart rates and are often not preceded by an increase in heart rate, an indicator of myocardial oxygen demand. In addition, the vast majority of these episodes of transient ischemia occurring out of hospital are asymptomatic. Therefore, ischemia induced in the hospital by exercise testing may not reflect the much more variable characteristics of ischemia occurring during normal activities out of hospital (figure 3).

There has been some controversy about the validity of ST segment changes seen during ambulatory Holter monitoring as markers of ischemia. However, the use of frequency-modulated recording systems in well-characterized patients with documented coronary artery disease and exercise-induced ischemia adds a greater measure of confidence to these changes as markers. Furthermore, recent work in which regional myocardial perfusion was assessed with rubidium-82 and positron-emission tomography in conjunction with electrocardiographic observations has further validated the use of ST segment depression as a marker of ischemia in such patients, even in the absence of symptoms.

The ambulatory monitoring studies in the group I patients with inducible ischemia on exercise confirmed the findings of several previous studies on the characteristics of ischemia during normal daily life in which similar techniques were used.
It was interesting to find that many exercise test variables that have been found to have considerable prognostic value, and that are accordingly regularly scrutinized in clinical practice, were not related to the level of this ischemic activity recorded during ambulatory monitoring. Many of these, such as exercise duration and hemodynamic parameters, are thought to largely reflect left ventricular dysfunction. The extent of this dysfunction will depend on resting ventricular function, the functional severity of the underlying coronary artery disease, the degree of resultant ischemia, and the level of workload imposed on the heart. Hence, these exercise parameters provide composite information on the severity of ischemia and its functional effects. It is therefore perhaps not surprising that they do not correlate well with observations from ambulatory monitoring, which measures only the electrocardiographic consequences of ischemia. For similar reasons it is perhaps also not surprising that it was the electrocardiographic changes associated with ischemia in the exercise tests that were related to the severity of ischemia during ambulatory monitoring out of hospital. Most of these exercise parameters have also been shown to have predictive value.

We are unable to find any relationship between the maximal depth of ST depression attained during exercise and ischemia out of hospital. This parameter has also been shown to be related to the anatomic severity of coronary artery disease, although its prognostic significance is uncertain and hence it may be unreliable as a quantitative index of ischemia. This study has also shown that the occurrence of anginal chest pain during exercise gives no indication of the severity of ischemic activity out of hospital and that the absence of chest pain on the other hand cannot be considered to indicate less active disease.

One important consideration in evaluating these data is that of variability. The responses to repeat exercise testing in the same patient may vary, although the myocardial workload threshold for ischemia is often constant. Despite possible variability in some exercise parameters, studies of the prognostic value of exercise testing have usually relied on one test to draw conclusions and this is also often the case in routine clinical practice. Considerable variability has also been noted during ambulatory monitoring studies. However, we endeavored to reduce this factor by monitoring the majority of patients for more than just one period of 24 hr while on consistent drug therapy, and also most studies were performed within a
short time of each other to ensure a clinical “steady state.”

The failure of a simple angiographic assessment of the severity of disease to predict the level of transient ischemia is not surprising since the assessment of coronary stenoses by percentage reduction in diameter is subject to considerable variation\(^3\) and may not accurately determine their real physiologic significance.\(^3\)

**Clinical implications.** There is growing evidence that active transient myocardial ischemia in patients with coronary artery disease is an indicator of risk and future coronary events.\(^3\),\(^3\) This study has highlighted the differences between indexes of transient ischemia in the exercise test and the much more variable characteristics of ischemia seen out of hospital during ambulatory monitoring. Even so, certain potentially useful new clinical features have emerged: (1) The presence or absence of angina during an exercise test cannot be used to assess the activity of ischemic events during daily life. (2) Patients with coronary artery disease but negative symptom-limited exercise tests for ischemia are most unlikely to experience active ischemia during daily life and this may explain the better prognosis in this group.\(^3\),\(^4\) (3) Similarly, patients who can exercise for 6 min or more on the Bruce protocol before showing signs of ischemia, those who develop ischemia only at heart rates of 150 beats/min or greater, and those in whom such ischemic changes have fully resolved by 5 or less minutes after exercise have very little or no ischemic activity out of hospital, which may also be reflected in a better prognosis.\(^3\),\(^7\) (4) In contrast, patients who develop ischemia after 6 min of exercise or less or at heart rates of less than 150 beats/min, and those in whom ischemic changes persist for more than 5 min after exercise, are likely to have much more active myocardial ischemia out of hospital, which may in turn be related to an adverse prognosis.\(^3\),\(^7\)

There is no indication that ambulatory monitoring of ischemic ST segment changes is superior to the exercise test for detection of ischemic heart disease, but it has provided a different picture of the pathophysiology of active transient myocardial ischemia, which is one of the potentially damaging aspects of coronary artery disease. The greater frequency and duration of transient ischemia out of hospital shown in our patients with lower ischemic thresholds and more persistent ischemia during exercise testing may explain the poorer prognosis in such patients.\(^3\),\(^7\) However, there was a wide range of ischemic activity out of hospital in these patients, which raises the possibility that characterizing such disease activity during daily life may be complementary to the findings of exercise testing and may help stratify these patients more precisely when trying to assess the risks of future coronary events.

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