Ischemia in the Ambulatory Setting—the Total Ischemic Burden: Relation to Exercise Testing and Investigative and Therapeutic Implications

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To establish the relation between treadmill exercise testing and ambulatory ST segment monitoring in the detection of ischemia in patients with coronary artery disease, and to assess whether standard medical therapy affects any such relation, 277 patients with stable angina and angiographically documented coronary artery disease were studied with treadmill exercise testing and 48 h ambulatory ST segment monitoring. One hundred forty-six patients (52%) were studied while receiving no routine antianginal therapy, and 131 (48%) while receiving standard medical therapy.

In 187 patients (67%) the exercise test was positive for ischemia. During 11,964 h of ambulatory monitoring, 881 episodes of ischemia (645 [73%] silent) were recorded, of which 809 (92%) occurred in patients with a positive exercise test. The mean heart rate at the onset of ischemic episodes during ambulatory monitoring was significantly less than that at the onset of 1 mm ST segment depression during exercise testing (94.5 versus 105.9 beats/min, p < 0.0001). However, the frequency of ambulatory ischemic episodes was strongly related to a positive exercise test (p < 0.0001), and this relation was similar for both silent and painful ischemia (p < 0.0001 for both) and in patients who were and were not receiving therapy (p < 0.0001 for both). The total duration of ischemia was similarly related to a positive exercise test (p < 0.0001). Only one patient with a negative exercise test had frequent (>5/day) episodes of ischemia on ambulatory monitoring and had documented coronary artery spasm.

Thus, exercise testing identifies the majority of patients likely to have significant ischemia during their daily activities. The strong relation between ischemia in the formal exercise and ambulatory settings suggests that the underlying pathophysiologic mechanisms are similar, even though the heart rate at the onset of ischemia in the two settings is different. There is little indication to perform ambulatory ST segment monitoring in patients with a negative exercise test unless the history suggests coronary artery spasm.

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Ischemia in the ambulatory setting (the "total ischemic burden") has generated considerable interest in recent times, particularly because it has been shown that the majority of episodes of significant ST segment change in patients with coronary disease occur in the absence of symptoms (1–3). Many studies have confirmed the ischemic nature of these episodes in patients with coronary artery disease (4,5), and silent and painful episodes of ischemia have been shown to be characteristically similar (1,6). It has been reported that the pathophysiologic mechanisms underlying the development of ischemia in the ambulatory setting may relate predominantly to a reduction in myocardial oxygen supply, rather than to an increase in myocardial oxygen demand, because the heart rate at the onset of ischemia in the ambulatory setting is significantly lower than that at the onset of 1 mm ST segment depression during exercise testing (7,8). If this is the case, one might not expect any particular relation between a positive exercise test and ischemia during the daily lives of patients, which, in turn, would have important investigative and therapeutic implications.

Clearly, if the mechanism of ischemia in the ambulatory setting is different from that of ischemia during exercise testing, ambulatory ST segment monitoring would be a complementary investigation for detecting ischemia in patients with coronary artery disease. Furthermore, if ischemia during the daily lives of patients with coronary disease was related predominantly to alterations in coronary vasomotor...
tone, it might be expected that calcium channel blocking agents would provide the greatest protective effect (9,10), and beta-adrenergic blocking agents might in certain circumstances aggravate the ischemic situation as a result of unopposed alpha-vasoconstriction (11,12).

We studied a large group of patients with coronary artery disease in an attempt to establish 1) whether there was any direct relation between the results of ambulatory ST segment monitoring and exercise testing, and 2) whether ambulatory ST segment monitoring contributed additional information to the results of exercise testing in detecting ischemia, as might be expected if it identified ischemia resulting from different mechanisms. The effects of standard antiangiinal therapy in altering any such relation between ambulatory monitoring and exercise testing were also assessed.

Methods

Study patients. Two hundred seventy-seven patients with angiographically documented coronary artery disease are included in this report. All patients had been referred for investigation of chest pain or a previous myocardial infarction. There were 231 men and 46 women, with a mean age of 55.5 years (range 30 to 77). All had significant coronary artery disease (78 single, 89 double and 110 triple vessel disease). One hundred sixteen patients had a previous myocardial infarction. All patients underwent treadmill exercise testing and 48 h of ambulatory ST segment monitoring. Investigations were performed in 146 patients while they were receiving no routine antiangiinal therapy, and in 131 when they were receiving standard antiangiinal therapy. Patients taking medication known to affect the ST segment, those with significant conduction disturbances and those unable to perform a treadmill exercise test were excluded from study. Also excluded were patients without at least one significant stenosis (>70%) of a major vessel. Abnormal rest ST/T wave changes were not considered an exclusion criterion for further study because, in the clinical setting, this is a common finding in patients presenting with chest pain.

All patients underwent cardiac catheterization performed by either the Judkins or the Sones technique. All coronary angiograms were independently reported by one of two radiologists. A significant stenosis was defined as ≥70% reduction in luminal diameter of a major vessel.

Exercise testing. All patients underwent maximal symptomatic-limited treadmill exercise testing using the modified Bruce protocol (13). Electrocardiograms were recorded at the onset and every 3 min of exercise and also with the development of chest pain or significant ST segment depression. A test was considered positive for ischemia if there was ST segment depression of ≥1 mm in magnitude from baseline, which was planar or downsloping and persisted for 0.08 s after the J point. Exercise was limited by the development of chest pain, breathlessness, exhaustion, and intermittent claudication, ventricular arrhythmias or hypotension.

Ambulatory ST segment monitoring. All patients underwent 48 h of ambulatory electrocardiographic (ECG) monitoring with pregelled electrodes to record two bipolar leads, anterior lead CM, and an inferior lead. The sites and method of application of these electrodes have been reported previously (14). Two channel ECG recordings were then obtained on magnetic tape with use of a frequency-modulated dual channel recorder (Oxford Medilog 2, frequency response 0.03 to 40 Hz). This system has adequate frequency response to accurately record and display the ST segment. The tapes were then visually analyzed at 60 to 120 times normal speed using an Oxford Medilog MA20 scanner, and all printouts were at 25 mm/s. Significant ST segment depression was defined as a planar or downsloping ST segment shift of ≥1 mm in magnitude from baseline measured 0.08 s after the J point and persisting for ≥30 s. Significant ST segment elevation was defined as ≥1 mm upward shift of the ST segment at the J point compared with the recording at rest.

Changes in T wave vector were not regarded as evidence of myocardial ischemia unless they were accompanied by significant ST segment changes.

During the period of ambulatory monitoring, all patients kept a detailed angina diary, recording the time of each episode of pain, the activity at the onset of symptoms and the requirement for nitroglycerin. An event marker on the ambulatory monitor was depressed at the onset of symptoms. This marked the magnetic tape so that the ECG playback would automatically display the ECG at that time. All patients were encouraged to continue with their normal daily activities during the period of monitoring.

Antiangiinal medications. One hundred thirty-one patients (48%) underwent investigation while receiving standard antiangiinal therapy. This consisted of a beta-adrenergic blocking agent (n = 104), a calcium channel blocking agent (n = 86) and nitrates (n = 62), either singly (n = 38) or in various combinations (n = 93), in addition to nitroglycerin as required. A further 146 patients were studied while taking no routine antiangiinal medication. In this group, those whose medications were stopped for the purposes of study had taken no routine therapy for at least 48 h; the others were studied before regular treatment was instituted. They took nitroglycerin as required, but not prophylactically during the study period.

Statistical analysis. The paired t test was used to compare the heart rates at the onset of 1 mm ST segment depression on exercise testing with the mean heart rate at the onset of ischemia during ambulatory monitoring. The Mann-Whitney U test was used to compare the frequency and duration of ischemic episodes per 24 h in patients with a positive exercise test and those with a negative exercise test.
Results

Heart rate changes. The mean heart rate at the onset of ischemic episodes on ambulatory monitoring was compared with that at the onset of 1 mm ST segment depression during exercise testing. The heart rate at the onset of ischemia during ambulatory monitoring was significantly less than that during exercise (94.5 versus 105.9 beats/min, p < 0.0001), and this difference was similar for both silent (93.8 versus 106.8 beats/min, p < 0.0001) and painful (96.2 versus 103.2 beats/min, p < 0.001) episodes of ischemia, and in patients who were not (99.2 versus 109.9 beats/min, p < 0.0001) and who were (86.1 versus 100.4 beats/min, p < 0.0001) receiving therapy.

Ambulatory monitoring and exercise testing (Fig. 1 and 2). One hundred eighty-seven patients (67%) had a positive exercise test for ischemia, and 881 ischemic episodes were recorded during 11,964 h of ST segment monitoring, of which 645 episodes (73%) were clinically silent. Figure 1 shows the relation between the results of exercise testing and the mean frequency of total ischemia on ambulatory monitoring in the 277 patients. Eight hundred nine episodes (92%) of ischemia recorded during the period of ambulatory monitoring occurred in patients with a positive exercise test; only 72 episodes (8%) occurred in patients with a negative exercise test. The frequency of total ischemic episodes per 24 h was strongly related to a positive exercise test (p < 0.0001).

Figure 2 shows the frequency distribution of total ischemic episodes in the 187 patients with a positive and the 90 patients with a negative exercise test. Only one patient with a negative exercise test had frequent (>5/day) ischemic episodes, and this patient had documented coronary artery spasm. In the absence of coronary spasm, 88 patients with a negative exercise test had a total of 51 episodes of ischemia (5.7%) of a mean duration of 7.5 min/24 h during 3,861 h of monitoring.

Role of antianginal therapy (Fig. 3). We also investigated the relation between ischemia on ambulatory monitoring and the results of exercise testing in 146 patients who were not and 131 patients who were receiving routine antianginal therapy. Although the frequency of ischemic episodes in the group receiving standard therapy was less than that in the group not receiving therapy, there was no alteration in the overall relation between ischemic episodes on ambulatory monitoring and a positive or negative exercise test. The frequency of ischemic episodes was again significantly related to a positive exercise test in both groups (p < 0.0001,
for both). There was a significant relation between the frequency of total ischemic episodes and stage to ischemia during exercise testing in both the group not receiving therapy (p < 0.001) and those receiving standard medical therapy (p < 0.05) when comparing patients whose exercise test was positive at <6 and >9 min.

Silent/painful ischemia and exercise testing (Fig. 4). The relation between both silent (n = 645) and painful (n = 236) episodes of ischemia and a positive or negative exercise test was assessed. Painful and silent ischemia were equally strongly related to a positive exercise test (p < 0.0001 for both).

Duration of ischemia and exercise testing. Figure 5 demonstrates the relation between the total duration of ischemic episodes/24 h and a positive or negative exercise test in the overall group of 277 patients and in the two subgroups (146 patients not receiving and 131 patients receiving therapy). The total duration of ischemic episodes/24 h was similarly related to a positive exercise test in all groups (p < 0.0001 for all three groups).

Sensitivity of ambulatory monitoring and exercise testing. Exercise testing had a sensitivity of 67% for detecting coronary artery disease and ambulatory ST segment monitoring a sensitivity of 54%. The addition of the information from 11,964 h of ambulatory ST segment monitoring increased the sensitivity of exercise testing from 67% to 74% for the combined investigations in detecting ischemia.

Discussion
Role of alterations in vasomotor tone in ambulatory ischemia. From this study, it would appear that the heart rate at the onset of ischemia in the ambulatory setting is, indeed, less than that at the onset of 1 mm ST segment depression during formal exercise testing, and this is true of both silent and painful episodes of ischemia. For many years, angina was assumed to result from an imbalance between myocardial oxygen supply and demand across a fixed coronary stenosis. This belief was tempered by reports (15-17) that reduction in myocardial blood flow due to coronary spasm at the site of "fixed stenosis" was responsible for many ischemic syndromes, and the demonstration (18) that the majority of coronary stenoses had an arc of normal arterial wall capable of dilation and constriction. Mudge et al. (19) showed that patients with stable exertional angina may manifest episodic vasoconstriction superimposed on fixed coronary lesions, and Yasue et al. (20) reported that there is a circadian pattern of coronary tone with a tendency to increased vasoconstriction in the morning. With the wide-
spread use of ambulatory ST segment monitoring, it has been reported (1,2,4,8,21,22) that the heart rate at the onset of daily ischemia is considerably less than that at the onset of exercise ischemia, as shown in this study. It has also been reported (4) that heart rate does not increase significantly before the majority of such ischemic episodes.

These findings have led many investigators to suggest that the primary underlying pathophysiologic mechanism of ambulatory ischemia is a reduction in myocardial oxygen supply due to alterations in coronary vasomotor tone. Quyyumi et al. (14) previously showed that a small but significant increase in heart rate precedes the majority of ischemic episodes during the daily lives of patients, and we have confirmed this finding (1). Although this discrepancy in heart rates between the two tests cannot be ignored, it may be that the method of assessing ischemia during exercise testing contributes partly to the differences in heart rates; the identification of 1 mm ST segment depression by performing ECGs only every 1 or 3 min or when significant ischemia appears to be present may obscure the true onset of ischemia. It has also been shown that, although the heart rate may not increase significantly before the onset of ischemic episodes during mental stress and other daily activities, there is an increase in systolic and diastolic blood pressure, which results in an increase in myocardial oxygen demand (23). Deanfield et al. (24) also showed that systolic blood pressure at the onset of spontaneous ischemic episodes mirrors that at the onset of exercise-induced ischemia. Thus, assessment of underlying pathophysiologic mechanisms solely on the basis of the change in heart rate may be flawed.

Role of beta-blockade in the mechanism of ambulatory ischemia. We previously showed (25) in subsets of patients that atenolol, a selective beta-adrenergic blocking agent with no coronary vasodilating activity, significantly reduces the frequency of ischemic episodes; others (26,27) have reported similar effects with other beta-blocking agents. In a recent multicenter randomized study of patients with angina, Stone et al. (28) reported that the addition of a calcium antagonist to a beta-blocker or nitrate, or both, had no effect on any measure of ambulatory ischemia in patients with classic exertional angina, and noted that episodic vasoconstriction may not be the only mechanism responsible for episodes of ambulatory ischemia. Furthermore, in a randomized study of metoprolol, nifedipine and their combination in chronic stable angina, Egstrup (29) showed that metoprolol significantly reduced the frequency and duration of ischemic episodes, and reported that the drug acted by reducing myocardial oxygen demand even during ischemic episodes observed in daily life, where impairments of myocardial oxygen supply are suspected. The benefits shown from beta-blockade in modifying transient ischemic episodes (25–31) do not support the concept that a reduction in myocardial oxygen supply plays a predominant role in transient ischemic episodes. In contrast, beta-blockade may reduce myocardial oxygen demand and thus make transient reductions in oxygen supply due to alterations in coronary vasomotor tone more tolerable (29). However, the underlying pathophysiologic mechanisms of ischemia are, in either the ambulatory or the formal exercise test setting, the relation between ischemia during exercise testing and during everyday activities suggests that the underlying mechanisms are similar, complex and likely to be multifactorial.

Ambulatory ECG monitoring versus exercise testing for identifying ischemia. Although ambulatory monitoring systems that faithfully reproduce the ST segment are becoming increasingly available, they are expensive and not freely available for routine clinical use. This study shows that we can identify the large majority of patients likely to have ischemia in the ambulatory setting by performing a standard exercise test, and that ambulatory monitoring adds little further information for detecting ischemia. In addition, whereas exercise testing had a sensitivity of 67% for the diagnosis of coronary artery disease, ambulatory ST segment monitoring had a sensitivity of only 54%. Campbell et al. (22) reported a 54% sensitivity for ambulatory monitoring in the detection of ischemia, and noted that, in those with a negative exercise test, there were no ischemic episodes. In a study of 210 patients with stable angina, Izivoni et al. (21)
reported that only 3 patients with a negative exercise test had evidence of ischemia on ambulatory monitoring. Quyyumi et al. (32) reported that ambulatory monitoring increases the sensitivity of exercise testing from 73% to 77% for the combined investigations. We have shown that despite almost 12,000 h of ambulatory monitoring, the sensitivity of exercise testing was increased by only 7% (to 74%) for the combined investigations in the detection of ischemia.

Prognosis of ambulatory ischemia. With continued research on ischemia during everyday activities, the quantification of ischemia may assume prognostic importance. Although silent myocardial ischemia in the setting of unstable angina or after myocardial infarction is associated with an adverse prognosis (33,34), we do not know the prognostic significance of ischemia in the ambulatory setting in patients with stable angina or whether medical therapy influences that prognosis. Recent evidence (35) suggests that in patients with coronary artery disease and a positive exercise test for ischemia, those with additional evidence of ischemia on ambulatory monitoring have an adverse prognosis compared with that in patients without ambulatory ischemia. If this were demonstrated in large scale trials, there would clearly be an indication to perform ambulatory ST segment monitoring to supplement the results of a positive exercise test and allow for risk stratification.

Diagnostic value of ambulatory ECG monitoring. Little diagnostic benefit is derived from performing ambulatory ST segment monitoring in patients with a negative exercise test (except in those with a history suggestive of coronary artery spasm or in patients who are unable to perform a meaningful exercise test). Also, the relation between ischemia in the ambulatory setting and that during exercise testing is preserved in patients receiving standard medical therapy. Again, for this group of patients, ambulatory monitoring appears to add little information to the results of exercise testing for identifying ischemia. Few patients receiving standard medical therapy were found to have frequent ischemia during their daily activities, attesting to the fact that standard medications are effective in treating the total ischemic burden (36).

Previous reports. Epstein et al. (37) previously suggested that patients with no ischemic changes during exercise or with ischemia only at high levels of exercise, rarely have silent ischemia on ambulatory monitoring. We (1) confirmed this finding in patients who were not receiving routine therapy, showing a strong relation between the frequency of silent ischemia and stage to 1 mm ST segment depression on exercise testing. This relation also exists when comparing the frequency of total ischemic episodes with stage to 1 mm ST segment depression on exercise testing in groups with and without routine antianginal therapy when comparisons are made between those patients with a positive test at <6 and >9 min of exercise. Quyyumi et al. (14) and Campbell et al. (22) also showed a significant relation between time to onset of ischemia during exercise testing and frequency and duration of ambulatory ischemic episodes in patients with stable angina, and both reported the infrequency or absence of daily ischemic episodes in patients with a negative exercise test. Vaghawalla Mody et al. (38) reported no significant correlation between time to onset of ischemia during exercise testing and total duration of ischemia on ambulatory monitoring; however, they note that their study group did not have uniformly proved coronary artery disease, which may have had a bearing on the correlation between manifestations of ischemia during the exercise test and those documented during ambulatory monitoring. They commented that the sensitivity and predictive accuracy of ambulatory ST segment monitoring was low, and that the quantification of the total ischemic burden by this method is of little diagnostic value in identifying the presence of coronary disease.

Implications. Our findings suggest that it is possible to assess the efficacy of different drug regimens by performing standard exercise testing. Although further work is necessary, it is likely that a drug that eliminates or significantly delays the onset of ischemia during exercise testing will have a beneficial effect on the frequency and duration of silent and painful ischemia during the patient's daily activities. When investigating the prognostic implications and other aspects of silent ischemia and the total ischemic burden, it is probable that a positive exercise test at a relatively low work load will have to be a prerequisite for inclusion in such studies. It is noteworthy that, despite the proposal that the pathophysiologic mechanisms of ambulatory ischemia result from different mechanisms from those causing ischemia during exercise testing, many investigators (3,4,8,24,39) have considered only patients with a positive exercise test when assessing the characteristics of ambulatory ischemia.

Conclusions. Silent and painful episodes of myocardial ischemia in the ambulatory setting appear to have underlying pathophysiologic mechanisms similar to those causing ischemia during standard exercise testing. Ischemic episodes during the daily lives of patients with coronary artery disease almost invariably occur in those with a positive exercise test, whether those patients are studied with or without antianginal therapy, and such episodes are rare and of short duration in those with a negative test. Ambulatory ST segment monitoring adds little to the results of exercise testing in detecting ischemia. There is little indication to perform ambulatory ST segment monitoring in patients with a negative exercise test, except in patients who have a history suggestive of coronary artery spasm.

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References