

Silent myocardial ischaemia in chronic stable angina: a study of its frequency and characteristics in 150 patients

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SUMMARY One hundred and fifty unselected patients with documented coronary artery disease were studied to establish the frequency and characteristics of silent myocardial ischaemia. Patients underwent ambulatory ST segment monitoring off all routine antianginal treatment (total 6264 hours) and exercise testing (n = 146). Ninety one patients (61%) had a total of 598 episodes of significant ST segment change, of which 446 (75%) were asymptomatic. Twenty seven patients (18%) had only painless episodes; 14 (9%) patients only painful episodes; 50 patients (33%) had both painless and painful episodes. The mean number of ST segment changes per day was 2.58 (1.95 silent); however, 11 patients (7%) had 50% of all silent episodes, and 48 patients (32%) had 91% of all silent episodes. Fifty nine patients (39%) had no ST segment changes on ambulatory monitoring, and 73 patients (49%) had no evidence of silent ischaemia. Episodes of silent ischaemia occurred with a similar circadian distribution to that of painful ischaemia, predominantly between 0730 and 1930. There was a similar mean rise in heart rate at the onset of both silent and painful episodes of ischaemia. Silent ischaemia was significantly more frequent in patients with three vessel disease than in those with single vessel disease, and was also significantly related to both time to 1 mm ST depression and maximal exercise duration on exercise testing. There was a highly significant relation between the mean number and duration of episodes of silent ischaemia in patients with positive exercise tests when compared with those with negative tests. No episode of ventricular tachycardia was recorded in association with silent ischaemic change.

It has been known for many years that myocardial infarction can occur in the absence of angina or its equivalents,^{1,2} and since the introduction of ambulatory ST segment monitoring it has become clear that ST segment depression, the electrocardiographic hallmark of ischaemia, is a common finding in patients with coronary artery disease and is "silent" in most of them.³⁻⁵ These silent ST segment changes have been shown to be truly ischaemic by various haemodynamic^{6,7} and radionuclide⁸⁻¹⁰ techniques.

The therapeutic and prognostic significance of silent myocardial ischaemia in patients with coronary artery disease and stable angina has yet to be elucidated. But if silent myocardial ischaemia is a

frequent event in patients with coronary artery disease, angina or its equivalents may no longer be the primary features to be considered before proceeding to percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, in view of the possible relation between silent ischaemia and both myocardial infarction¹¹⁻¹³ and sudden death.^{11,14,15}

We studied 150 unselected patients with documented coronary artery disease off routine antianginal medications to establish the frequency and characteristics of silent myocardial ischaemia. Previous studies have reported smaller numbers, and some studies used highly selected patients.

Patients and methods

We studied 150 unselected patients with angiographically confirmed coronary artery disease. All patients had been referred for investigation of chest

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pain, or after myocardial infarction. There were 121 men and 29 women (mean age 55 years, range 33–77 years). All had clinically significant coronary artery disease. Sixty one patients had had at least one myocardial infarction. All patients underwent 24–48 hours of ambulatory ST segment monitoring off all routine antianginal medications, and 146 performed exercise testing according to the modified Bruce protocol. For each individual we recorded the details of anginal history, history of previous myocardial infarction, and previous angioplasty or coronary artery bypass surgery. We recorded the details of the resting electrocardiogram, left ventriculogram, coronary anatomy, and left ventricular ejection fraction.

EXERCISE TESTING

One hundred and forty six patients underwent maximal symptom limited treadmill exercise testing according to the modified Bruce protocol. Three patients were unable to exercise because of severe intermittent claudication and one could not cope with the treadmill. Electrocardiograms were recorded at the start of exercise and every three minutes thereafter and whenever chest pain, hypotension, or significant ST segment depression developed. A test was considered to be positive if there was ST segment depression of ≥ 1 mm which was planar or down-sloping and persisted for 0.08 s after the J point. Exercise was limited by the development of chest pain, dyspnoea, exhaustion, complex ventricular arrhythmias, or hypotension.

AMBULATORY ST SEGMENT MONITORING

All patients underwent 48 hours of ambulatory ST segment monitoring with pre-gelled electrodes to record two bipolar leads, an anterior lead CM5, and an inferior lead. The sites and method of application of these electrodes have been described elsewhere.¹⁶ Two-channel recordings were then obtained on magnetic tape by a frequency modulated dual-channel recorder (Oxford Medilog 2, frequency response 0.05–40 Hz). The frequency response of this system is sufficient to record and display the ST segment accurately. The tapes were then visually analysed at 60 times normal speed by an Oxford Medilog MA20 scanner, and all printouts were at 25 mm/s. Significant ST segment depression was defined as planar or down-sloping ST segment shift of ≥ 1 mm measured 0.08 s after the J point that persisted for > 30 s. Significant ST segment elevation was defined as an upward shift of the ST segment of ≥ 1 mm at the J point compared with the resting recording. Changes in the T wave vector were not regarded as evidence of myocardial ischaemia unless they were accompanied by significant ST segment changes.

During the period of ambulatory monitoring, all patients kept a detailed angina diary to record the time of each episode of pain, the activity at the onset of symptoms, and the requirement for glyceryl trinitrate. They pressed an event marker on the ambulatory monitor at the onset of symptoms. This marked the magnetic tape, which meant that the electrocardiographic playback would automatically display the electrocardiogram at that time. All patients were encouraged to continue their normal activities during the period of monitoring.

COLLECTION OF DATA DURING AMBULATORY MONITORING

The following details were extracted and incorporated in the data bank: the heart rate immediately before and at the onset of each episode of ischaemia; the duration of each episode; maximal ST segment change; the relation of each episode to symptoms; the presence of arrhythmias, and whether they occurred in association with silent or painful episodes.

CARDIAC CATHETERISATION

In all patients we used either the Judkins or Sones technique for cardiac catheterisation. All angiograms were reported on independently by one of two senior radiologists, and a random selection were further reviewed by a cardiologist. Stenoses that reduced the luminal diameter of a major vessel by $\geq 70\%$ were regarded as significant. For the purposes of classification, significant left main coronary artery disease was regarded as two vessel disease.

The left ventricular ejection fraction was measured by a standard method, with two-frame analysis of the left ventriculogram in the right anterior oblique position.

STATISTICAL ANALYSIS

Bivariate statistics—We tested for the significance of relations between silent ischaemia and the variables of interest by non-parametric analysis. The Mann-Whitney U test, the Kruskal-Wallis test, or the Wilcoxon matched pairs signed ranks test was used, as appropriate.

Multivariate statistics—Discriminant function analysis was performed to ascertain which variables could be used to predict the frequency of silent ischaemia on ambulatory monitoring.

Results

FREQUENCY, DURATION, AND SEVERITY OF SILENT AND PAINFUL ISCHAEMIA

Five hundred and ninety eight episodes of significant ST segment change were recorded during 6264 hours of ambulatory ST segment monitoring. Four

hundred and forty six episodes (75%) were asymptomatic. The mean duration of attacks (20.8 v 21.6 min) and mean severity of ST segment change (1.54 v 1.89 mm) were similar in both painless and painful episodes, as was the mean heart rate at the onset of both painless and painful episodes (95 v 99 beats/min). There was a significant increase in mean heart rate at the onset of both silent (86–95 beats/min, $p < 0.001$) and painful (88–99 beats/min, $p < 0.001$) ischaemia. There was no increase in heart rate at the onset of ischaemia in 163 instances (128 silent (29%), 35 painful (23%)). The mean number of ischaemic episodes per day was 2.58 of which 1.95 were silent. Fifteen (10%) patients had five or more episodes of silent ischaemia per day.

RELATION BETWEEN ISCHAEMIC CHANGES AND SYMPTOMS

Figure 1 shows the relation between ischaemic change on ambulatory monitoring and symptoms. Ninety one patients (61%) had one or more episodes of ischaemia. Fifty (33%) had mixed painful and painless episodes, and 27 (18%) had painless episodes only. Fifty nine patients (39%) had no ischaemic changes during 2548 hours of monitoring, and 73 patients (49%) had no silent ischaemic changes. Fifteen (10%) patients had 50% of all episodes of ischaemia, and 60 (40%) had 90% of total episodes. Eleven patients (7%) had 50% of episodes of silent ischaemia and 48 patients (32%) had 91% of the episodes of silent ischaemia (fig 2).

RELATION OF SILENT ISCHAEMIA TO CORONARY ANATOMY

Forty six patients (31%) had single vessel, 37 (25%) two vessel, and 67 (44%) three vessel coronary artery disease. Episodes of silent and total ischaemia were significantly more common in three vessel disease than in one vessel disease ($p < 0.05$) (fig 3). Mean ST segment depression in those with three vessel disease was also significantly greater during attacks than in those with single vessel disease ($p < 0.001$).

RELATION OF SILENT ISCHAEMIA TO EXERCISE TESTING

One hundred and forty six patients underwent treadmill exercise testing. One hundred and one (69%) patients had a positive test for ischaemia. Sixty four patients (63%) with a positive exercise test had at least one episode of silent ischaemia on monitoring. Eleven (25%) of the 45 patients with a negative exercise test had one or more episodes of silent ischaemia. Figure 4 shows the frequency distribution of silent ST segment change throughout the day. Only 15 (10%) patients had ≥ 5 episodes of silent ischaemia per day, and 14 (93%) of these had a positive exercise test at less than six minutes of exercise. One patient with a negative exercise test had documented coronary artery spasm.

We compared the mean heart rates at the onset of silent ischaemic change on monitoring with heart rate at 1 mm ST segment depression on exercise in 64 patients. The onset heart rate on ambulatory monitoring

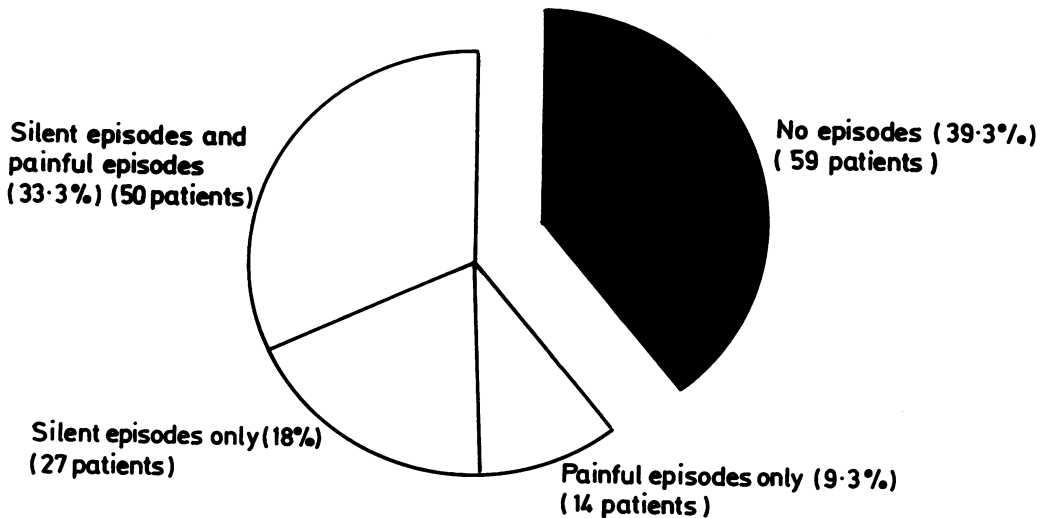


Fig 1 Pie chart showing the percentage frequency of painless and painful ischaemia during 6264 hours of ST segment monitoring in 150 unselected patients with coronary artery disease.

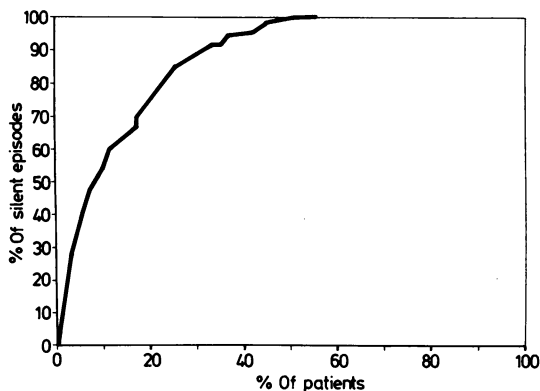


Fig 2 Diagram showing the cumulative frequency of silent ischaemic episodes per day in 150 unselected patients with coronary artery disease. Over 50% of episodes occurred in 7% of patients and over 90% occurred in 32% of patients.

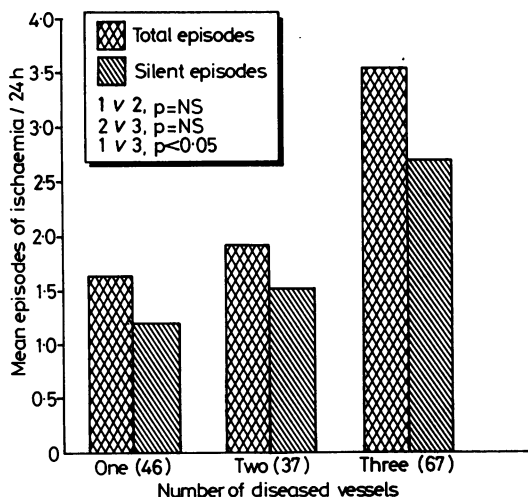


Fig 3 Bar chart showing the mean frequency of total and silent ischaemic episodes per day in patients with coronary artery disease of different severity.

toring was significantly lower than that on exercise testing (99 *v* 110 beats/min, $p < 0.001$).

In the 101 patients with a positive test the mean number of episodes of silent ischaemia per day was 2.55 (range 0–33), compared with 0.67 (range 0–15) in those with a negative test ($p < 0.001$). The mean duration of episodes of silent ischaemia per 24 hours was 54 minutes (range 0–554 min) in those with a positive test, compared with a mean of 9 min (range 0–109 min) in those with a negative test ($p < 0.001$).

There was a significant relation between the mean number and duration of silent ischaemic episodes per

Mulcahy, Keegan, Crean, Quyyumi, Shapiro, Wright, Fox

day and (a) the exercise stage achieved before 1 mm ST segment depression developed ($p < 0.01$, $p < 0.01$ respectively) (fig 5) and (b) the time to maximal exercise ($p < 0.001$, $p < 0.01$ respectively).

We divided the positive exercise tests into those with < 2 mm and those with ≥ 2 mm ST segment depression, and we compared the mean number and duration of episodes of silent ischaemia on ambulatory monitoring in the two subgroups. No significant differences were noted. There was no association between the frequency of silent ischaemia and time taken for the electrocardiogram to become normal after exercise.

We compared the mean frequency and duration of episodes of silent ischaemia with the stage to maximal exercise in 45 patients with a negative exercise test. This confirmed a low frequency and duration of silent ischaemia in the subgroup as a whole, irrespective of stage to maximum exercise. Of the 43 episodes (9.6%) of silent ischaemia recorded in this group, 15 (35%) occurred in one patient with coronary spasm.

RELATION OF SILENT ISCHAEMIA TO LEFT VENTRICULAR EJECTION FRACTION AND A HISTORY OF MYOCARDIAL INFARCTION

The 89 patients who had not suffered a previous myocardial infarction tended to have an increased frequency of silent ischaemic episodes ($p = 0.072$) that lasted significantly longer ($p < 0.05$) than silent episodes in the 61 patients who had suffered one or more previous infarctions. The frequency of silent ischaemia was also inversely related to the presence of dyskinetic/akinetic areas on the left ventriculogram ($p < 0.01$). There was no relation between left ventricular ejection fraction and silent ST segment change.

RELATION OF SILENT ISCHAEMIA AND THE FREQUENCY OF VENTRICULAR ARRHYTHMIAS

Thirteen patients (8.6%) had one or more recorded episodes of ventricular arrhythmia (ventricular bigeminy, multifocal ventricular extrasystoles, ventricular couplets, or ventricular tachycardia) during the 6264 hours of ambulatory monitoring. Six patients had episodes of unsustained ventricular tachycardia; however, none occurred in association with silent ischaemia.

CIRCADIAN DISTRIBUTION OF SILENT ISCHAEMIC EPISODES

Figure 6 shows the distribution of episodes of both total and silent ischaemia. Most episodes (67% of the total, 67% of the painless, and 68% of painful episodes) occurred in the twelve hour period between 0730 and 1930.

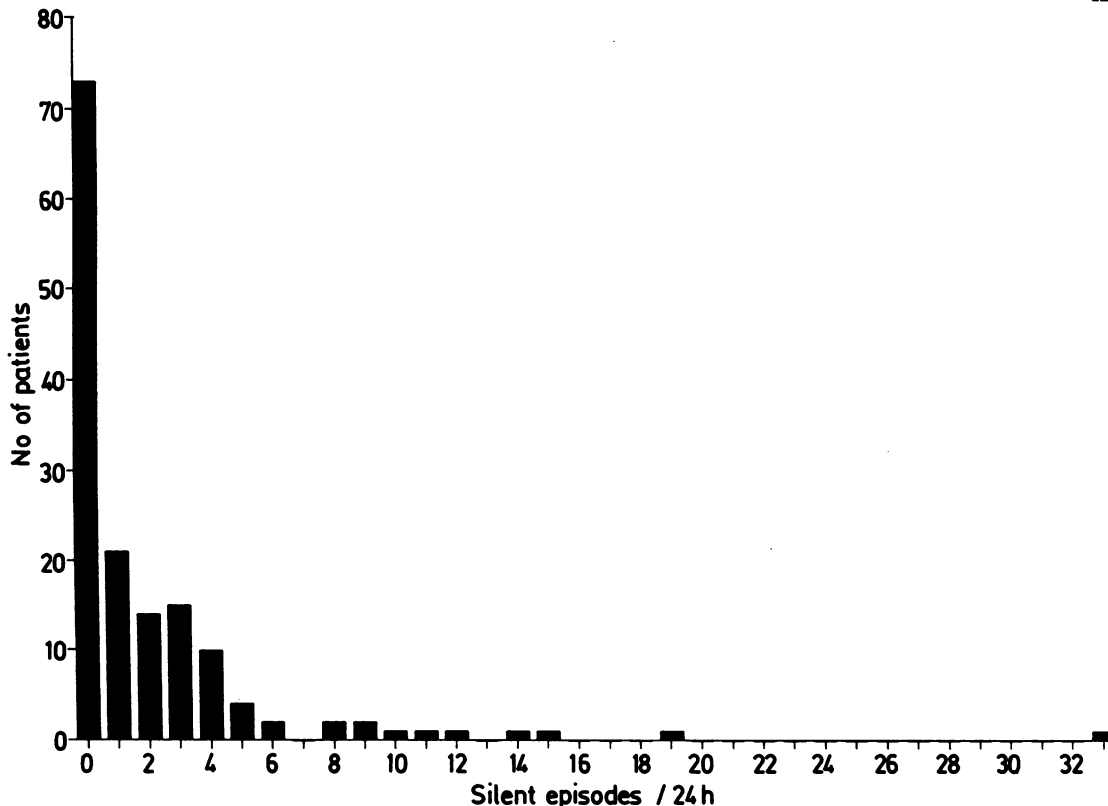


Fig 4 Frequency distribution of silent ischaemic episodes per day in 150 unselected patients with coronary artery disease.

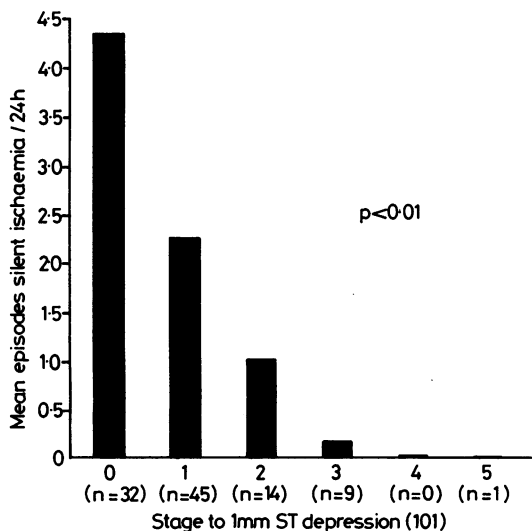


Fig 5 Bar chart showing the relation between the mean episodes of silent ischaemia per day and stage to 1 mm ST segment depression on exercise testing.

MULTIVARIATE ANALYSIS

To attempt to identify predictors of silent ischaemia we performed a stepwise discriminant function analysis with five variables (exercise test, maximal time of exercise test, previous myocardial infarction, number of vessels diseased, and left ventricular ejection fraction). As in the univariate analysis, the exercise test accounted for almost all the discriminating power in predicting the presence of silent ischaemia.

Discussion

This study describes the frequency, characteristics, and associations of silent myocardial ischaemia in patients with coronary artery disease. We have described a study population that differs from those of many previous investigators; our patients were unselected and the only criterion for inclusion in the study was clinically significant coronary artery disease. We can confirm earlier reports that silent ischaemia is common, and indeed 75% of all episodes of significant ST segment change were asymp-

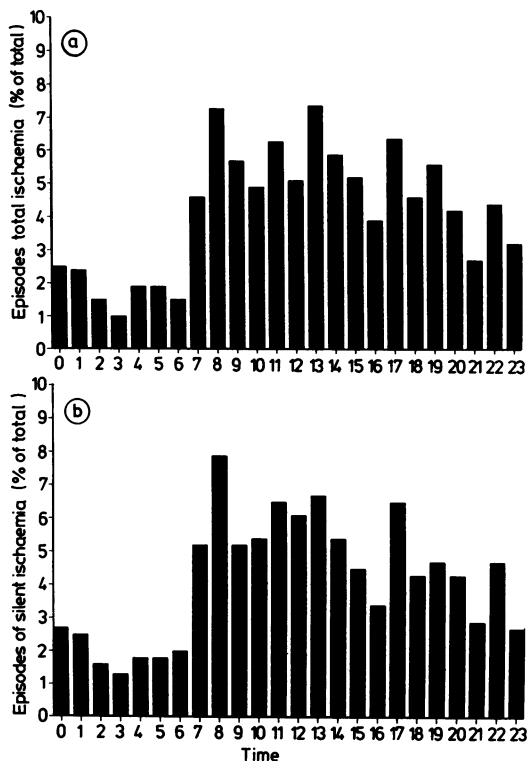


Fig 6 Bar chart showing (a) the circadian distribution of total ischaemic episodes and (b) the circadian distribution of silent ischaemic episodes in 150 unselected patients with coronary artery disease.

tomatic. Until now the frequency distribution of silent ischaemic episodes has not been examined in detail, and it has been suggested that most patients with angina may have frequent episodes of silent ischaemia.¹⁷ We found that silent ischaemia was frequent in a small but appreciable proportion of the population of patients with coronary artery disease; however, almost half of the patients had no evidence of silent ischaemia on up to 48 hours of ambulatory monitoring, and over half of all silent ischaemic episodes occurred in only 7% of the patients.

We also examined the pathophysiological causes of silent myocardial ischaemia. The exact mechanisms by which silent ischaemia occurs are unknown, but many workers have reported that out of hospital episodes of ischaemia occur at a lower heart rate than the heart rate at the onset of 1 mm ST segment depression on exercise testing^{8,18,19} and that this suggests that an increase in vasoconstrictor tone in the coronary vessels contributes to the genesis of ischaemia.¹⁹ Rozanski *et al.*, however, point out that although the heart rate at the onset of ischaemia is

lower during mental stress than during exercise, there are substantial increases in systolic and diastolic blood pressure that increase the afterload to values seen during exercise and that catecholamine secretion, and possibly its rate of rise, might further contribute to significant increases in myocardial oxygen demand during stress, even if an increase in oxygen demand is not suggested by the change in heart rate.²⁰ We found that silent ischaemia does indeed occur at a lower heart rate than that at the onset of ischaemia on exercise testing, as also does ST change accompanied by angina. ST segment monitoring showed that the increases in heart rate to silent or painful ischaemia were not different. Also a similar proportion of silent and painful episodes of ST segment depression occurred in the waking hours. These findings indicate that the pathophysiological mechanisms of silent ischaemia do not differ from those of painful ischaemia. We found an increase in heart rate before the onset of ST segment depression in most episodes of ischaemia; but in approximately one quarter of instances heart rate did not increase before either the silent or the painful episodes.

Thus the same mechanisms seem to cause painful and painless myocardial ischaemia; and so drugs that are effective in the relief of angina should also be effective in the treatment of silent ischaemia, as has indeed been shown.²¹

The occurrence, frequency, and duration of silent ischaemia correlated most closely with the exercise test. The frequency and duration of silent ischaemia increased considerably in those patients with a positive exercise test at low workloads, thus confirming the findings of Quyyumi *et al.*¹⁶ and Cambell *et al.*²² Indeed, in those patients whose exercise test was not positive until after stage 2 of the modified Bruce protocol, or whose exercise test was negative, silent ischaemia was very uncommon, which supports the assertion of Epstein *et al.*²³

We also found a relation between the frequency of silent ischaemia and the extent of coronary artery disease, as did Kunkes *et al.*²⁴ This might be expected because the exercise test has been shown to correlate loosely with the extent of coronary disease. This relation, however, is much less close than that between silent ischaemia and the exercise test.

Interestingly, patients without a previous history of myocardial infarction had a non-significant trend towards more frequent episodes of silent ischaemia that lasted significantly longer than in patients with a history of myocardial infarction. This may be because patients who have suffered one or more previous myocardial infarctions have less viable myocardium capable of becoming ischaemic, and this is supported by the finding of significantly less silent ischaemia in patients with dyskinetic/akinetic seg-

ments on left ventriculography. Another explanation is that the electrocardiographic effects of previous myocardial infarction obscure alterations in the ST segment.

Finally, this study confirms that ventricular arrhythmias are relatively uncommon in unselected patients with coronary artery disease.²⁵ While a causative relation between silent ischaemia and ventricular irritability might be expected, this was not found in our subjects.

The results of this study do not imply that silent ischaemia is unimportant in clinical practice; however, it seems that silent ischaemia is probably most important in a small proportion of the population of patients with coronary artery disease. Where facilities for ambulatory monitoring are limited or not available, exercise testing should provide a means of identifying the majority of such patients, particularly if the test is positive at low workloads. Further studies will be necessary to determine the prognostic implications of silent ischaemia in patients with chronic stable angina, and whether the prognosis can be altered by medical or surgical treatment.

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