

## Morphology of ambulatory ST segment changes in patients with varying severity of coronary artery disease *Investigation of the frequency of nocturnal ischaemia and coronary spasm*

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**SUMMARY** The frequency and magnitude of objectively determined myocardial ischaemia during normal daily activities of patients with varying severity of coronary artery disease are unknown. Furthermore, the incidence of nocturnal resting myocardial ischaemia and frequency of coronary spasm in patients with normal coronary arteries and chest pain are also not known. One hundred consecutive patients with chest pain referred for coronary angiography were therefore investigated with exercise testing and ambulatory ST segment monitoring. Fifty two of 74 patients with significant coronary artery disease and six of 26 with no significant coronary narrowing had episodes of ST segment change during 48 hours of ambulatory monitoring. Two patients, one with normal coronary arteries and localised spasm and one with three vessel disease, had episodes of ST segment elevation, whereas all other patients had episodes of ST segment depression. The frequency, duration, and magnitude of ST segment changes were greater in patients with more severe types of coronary artery disease. Thus more than six episodes of ST segment change per day occurred in patients with two or three vessel disease or left main stem stenosis and in the only patient with coronary spasm and normal coronary arteries. Nocturnal ischaemia occurred in 15% of patients with coronary artery disease and was almost an invariable indicator of two or three vessel coronary artery disease or left main stem stenosis. Episodes of ST segment change occurred most commonly during the morning hours and least commonly during the night, in parallel with changes in basal hourly heart rates. The heart rate at the onset of ST segment change tended to be lower in patients with coronary artery disease than in those with normal coronary arteries. The duration of exercise to ST segment depression tended to be shorter in patients with more severe disease, but it could not predict patients with nocturnal myocardial ischaemia, left main stem stenosis, or coronary spasm, whereas ambulatory ST segment monitoring was able to identify most of these patients.

Several non-invasive techniques have been used in clinical practice for diagnosing the presence and severity of coronary artery disease.<sup>1,2</sup> A typical history of chest pain and an abnormal resting electrocardiogram are sometimes sufficient to diagnose the presence of coronary artery disease, but its severity cannot be determined by this means. Exercise testing and radioisotope imaging have been used to determine the presence of disease in those patients in whom the his-

tory is atypical and the resting electrocardiogram normal.<sup>1-3</sup> Exercise testing also determines the functional consequence of coronary artery disease, and radioisotope scanning provides an index of the size of the ischaemic myocardium, but the severity of underlying coronary artery disease often cannot be determined.<sup>1,4</sup> Ambulatory electrocardiographic ST segment monitoring has been used in several recent studies<sup>5-14</sup> to identify the frequency of myocardial ischaemia in patients with coronary artery disease, but the type and extent of these changes in patients with differing severity of coronary artery disease have not been fully evaluated.

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Improvements in the recording and reproduction of low frequency signals in ambulatory electrocardiographic systems<sup>15</sup> have provided an opportunity to study ST segment changes in different groups in the population. This study was designed to investigate in detail the frequency, duration, magnitude, and morphology of ST segment shifts in consecutive patients undergoing diagnostic coronary arteriography. We determined the frequency of daytime and nocturnal rest angina and of coronary artery spasm in patients with significant coronary artery disease. We also studied the relation between heart rate changes and the onset of ST segment shifts during ambulatory monitoring and compared them with heart rate changes at the development of ST segment depression during conventional exercise testing.

### Patients and methods

#### STUDY POPULATION

We studied 100 (74 men, 26 women; mean (SD) age 53.2 (9) years) consecutive patients with chest pain undergoing diagnostic coronary arteriography who were referred to one consultant cardiologist at this hospital between June 1982 and March 1983. Patients with atrial fibrillation, severe conduction defects on the electrocardiogram, gross left ventricular hypertrophy, those taking digoxin, and those with severe valvar heart disease were excluded. The duration of chest pain was <3 months in seven patients, 2–12 months in 16, and >1 year in 77. Ninety one patients complained of chest pain which was considered typical of angina pectoris and nine had atypical chest pain. A history of previous myocardial infarction with electrocardiographic evidence of Q waves or extensive loss of R wave was present in 27 patients, and a further 21 patients had ST-T wave abnormalities on the resting electrocardiogram. Informed consent was obtained from all patients.

#### STUDY PROTOCOL

After admission to hospital, all the patients antianginal medications were withdrawn for a period of 48 hours before investigations were started. Glyceryl trinitrate was given for pain. Patients were encouraged to be mobile around and outside the hospital during the period of the study unless they were experiencing frequent chest pains with minimal activity. Forty eight hour ambulatory monitoring and exercise testing were performed, and angina diaries were kept by all patients.

#### AMBULATORY MONITORING

A two channel recording was obtained using two pairs of bipolar electrodes which were applied precordially. In all patients one channel recorded lead CM5 with

the indifferent electrode over the manubrium and the exploring electrode in the precordial 5 position. The other channel recorded inferior changes resembling aVF in 35 patients with the exploring electrode at the xiphisternum and the indifferent electrode at the left sternoclavicular joint; in the other 65 patients the second channel recorded inferior forces by an arrangement in which the indifferent electrode was placed on the right of the manubrium and the exploring electrode over the left iliac fossa: the appearances resemble those seen in lead II. In all patients, a ground electrode was placed over the lower ribs on the right. Electrode jelly and gauze were used initially to abraid the skin until a sufficiently low skin impedance reading was obtained using an Oxford X1-1 electrode impedance tester. Monitor leads were attached to the electrodes (Red Dot 3M) and secured with adhesive tape. A 24 hour, two channel recording was then obtained on magnetic tape using a frequency modulated recorder (Oxford Medilog 2, frequency response 0.05–40 Hz). The tapes were then visually analysed at 60 times normal speed (Oxford Medilog MA20 scanner) and the areas of interest printed out at 25 mm/s.

Significant ST segment depression was defined as planar or downsloping shift of the ST segment of  $\geq 1$  mm in magnitude measured 0.08 s after the J point and persisting for at least 30 s. Significant ST segment elevation was defined as an upward shift of the ST segment of  $\geq 1$  mm in magnitude at the J point compared with the resting recording. At the beginning of each recording in 50 patients, the electrocardiogram was recorded with the patient in various positions, including standing, sitting, lying, supine, and in the left and right lateral positions, and after hyperventilation. None of the patients developed significant ST segment depression with changes of posture, but T wave changes occurred commonly and changes in T wave vector were not regarded as evidence of myocardial ischaemia unless they were also accompanied by significant ST segment shift. The electrocardiogram immediately preceding ST segment change, at the onset of ST segment change, and at the time of chest pain was printed out and heart rate measurements were made.

#### ANGINA DIARIES

Patients were instructed to keep diaries during the 48 hour monitoring period, during which they noted the time of onset and severity of chest discomfort and the activity at the time of pain. An event button was also pressed at the time of the onset of chest pain, which marked the magnetic tape so that the electrocardiographic playback would automatically display the electrocardiogram at that time.

#### EXERCISE TESTING

Exercise testing was performed in 99 of the 100

patients on a treadmill according to the modified Bruce protocol. Twelve lead electrocardiograms were recorded before and at the end of every three minutes during the test. More frequent recordings were made if the patient developed chest pain, hypotension, or significant ST segment depression. Blood pressure was measured with a mercury sphygmomanometer. The test was considered positive if there was ST segment depression of  $\geq 1$  mm in magnitude which was planar or downsloping and persisted for 0.08 s after the J point. One patient was having frequent pain at rest with ST segment changes and was therefore not exercised. Maximal exercise tests were performed using a treadmill during which exercise was limited by the appearance of chest pain, dyspnoea, fatigue, multiple ventricular extrasystoles, or hypotension.

#### ANGIOGRAPHY

Contrast left ventriculography and coronary arteriography were performed to obtain five views of the left coronary and at least two views of the right coronary arteries. The angiograms were reported independently by the radiologists, who were unaware of the results of other investigations. A significant lesion was defined as luminal narrowing in one or more of the major coronary arteries of  $\geq 70\%$  in magnitude. Left main stem stenosis was classed as two vessel disease. Five patients with normal coronary arteries had ergonovine provocation in which a mean dose of 0.6 mg was given intravenously and the angiograms were repeated.

#### Results

##### AMBULATORY ST SEGMENT MONITORING AND SEVERITY OF CORONARY ARTERY DISEASE

Of the 100 patients monitored, 58 developed 294 episodes of reversible ST segment changes during each 24 hour period of ambulatory monitoring. Five patients had no significant coronary artery disease at angiography, one had normal coronary arteries and localised spasm induced at angiography, and 52 had

varying severity of coronary artery disease (Table 1). Fifty six patients developed episodes of reversible ST segment depression only, whereas two had episodes of ST segment depression and elevation. The number of episodes of ST segment change varied from 1 to 66 in a 48 hour period and the duration varied from 2 minutes to 16 hours 40 minutes. The maximum magnitude of ST segment depression varied between 1 and 5 mm and ST segment elevation between 1 and 6 mm.

##### ST SEGMENT CHANGES IN RELATION TO SEVERITY OF CORONARY ARTERY DISEASE

One patient with three vessel disease and one with normal coronary arteries and localised coronary spasm in the left circumflex coronary artery had episodes of ST segment elevation and depression during ambulatory monitoring. All other patients had episodes of ST segment depression only. The frequency and duration of episodes of ST segment change were generally greater in patients with more severe coronary artery disease (Table 1). Patients with no significant coronary artery disease or coronary spasm had 2 (1.6) episodes lasting 44 (57) minutes per 24 hours compared with patients with three vessel disease who had 7.3 (9.2) episodes of ST segment shift lasting 99 (119) minutes per day. These differences were, however, not statistically significant (Table 1, Fig. 1). Patients with more than six episodes of ST segment change in a day had two or three vessel disease or spasm with normal coronary arteries (Fig. 1). Indeed, 20% of all patients with two or three vessel disease had more than six episodes of ST segment change during a 24 hour period. The duration of ST segment change and the maximum magnitude of ST segment depression also tended to increase with increasing severity of coronary artery disease (Table 1), but differences between the groups were not statistically significant. Seven patients with left main stem stenosis were studied. Six of these patients also had stenoses in the right coronary artery. The number of episodes and the duration of ST segment changes in

Table 1 Frequency, duration, and magnitude of the episodes of ST segment change during ambulatory electrocardiographic monitoring in 100 patients with varying severity of coronary artery disease and nocturnal angina. Values are mean (SD)

	Coronary artery disease					Nocturnal angina	
	Not significant	Spasm only	1 vessel	2 vessel	3 vessel	Left main stem stenosis	
Total No of patients	25	1	22	22	30	7	12
With ST segment changes (%)	5 (19)	1	11 (50)	17 (77)	24 (80)	7 (100)	12 (100)
Total No of episodes	2 (1.6)	1.8	2.9 (1.9)	3.7 (4.4)	7.3 (9.2)	17 (13)	12 (8.6)
Duration of episodes	44 (57)	7 (4)	63 (52)	59 (73)	99 (119)	174 (65)	3.8 (1.6)
Mean maximum ST change (mm)	1.5 (0.5)	1.6 (0.5)	1.1 (0.3)	2.5 (1.1)	2.3 (1.5)	3.8 (1.6)	3.4 (1.4)

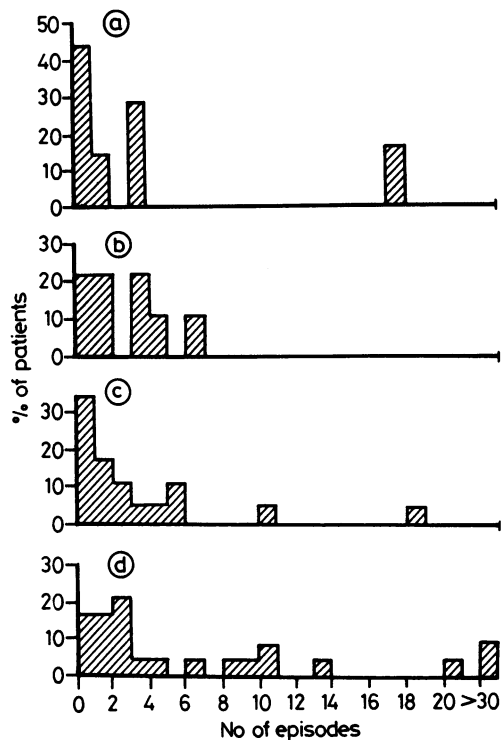


Fig. 1 Frequency of transient ST segment changes (number of episodes) in patients with (a) no significant disease, (b) one vessel disease, (c) two vessel disease, and (d) three vessel disease.

these patients tended to be greater than in any other group of patients (Table 1). Six of the seven patients with left main stem stenosis also had nocturnal ST segment changes.

NOCTURNAL ST SEGMENT CHANGES

Twelve patients with nocturnal ST segment changes were identified during ambulatory monitoring. A mean of 2.8 (1.8) episodes of ST segment shift occurred between midnight and 06.00 in this group of patients. These patients also had more frequent episodes of ST segment change (12 (8.6)) during the daytime when compared with any individual coronary

artery disease group (Table 1). Nine patients had three vessel disease, two had two vessel disease, of whom one had left main stem stenosis, and only one had normal coronary arteries and confirmed coronary spasm. Both patients with episodes of ST segment elevation had nocturnal episodes. The duration and magnitude of the episodes of ST segment change in patients with nocturnal angina were also greater when compared with individual coronary artery disease groups (Table 1). All patients with coronary artery disease and nocturnal angina who were exercised had positive exercise tests at low workloads (Table 2). Seven patients developed significant ST segment depression within three minutes and three within six minutes of exercise (mean 2.8 (1.1) minutes) (Table 3).

HEART RATE RELATION TO ST SEGMENT CHANGES

The heart rate at the onset of the episodes of ST segment change was also measured (Table 3). There was a wide variation in the heart rate at the onset of ST segment depression between episodes in the same patient and also between patients with the similar severity of coronary artery disease. The mean heart rate before ST segment depression occurred tended to be higher (123 (10) beats/min) in the five patients with normal coronary arteries than in those patients with coronary artery disease (101 (12) beats/min) (NS). There was no significant difference between the mean heart rates at the onset of ST segment depression in patients with one, two, and three vessel disease (Table 3) (mean range 99–105 beats/min). Nevertheless, patients with left main stem stenosis and those with nocturnal angina tended to develop ischaemia at relatively lower mean heart rates of 89 and 91 beats/min (Table 3) respectively.

The distribution of the episodes of ST segment change during the day and night in patients with coronary artery disease was also investigated (Fig. 2). Most of the episodes of both painful and painfree ST segment changes occurred during the morning and early afternoon. Relatively fewer episodes occurred in the evening, and the fewest episodes occurred at night. The diurnal variation in the mean hourly heart rates in 15 patients with no significant coronary artery

Table 2 Duration of exercise tests to 1 mm ST segment depression in patients with varying severity of coronary artery disease and nocturnal angina. Figures are numbers of patients

Duration of exercise (mins)	Coronary artery disease						Nocturnal angina
	Not significant	Spasm only	1 vessel	2 vessel	3 vessel	Left main stenosis	
3	0	0	3	4	14	4	7
4-6	2	0	4	9	8	2	3
7-9	1	0	4	3	1	0	0
>9	2	0	2	1	0	0	0
Negative test	20	1	9	5	6	0	1

Table 3 Heart rate at the onset of episodes of ST segment changes during ambulatory electrocardiographic monitoring in relation to the duration of exercise to and heart rate at the onset of 1 mm ST segment depression during exercise testing in patients with varying severity of coronary artery disease and nocturnal angina. Values are mean (SD)

	Coronary artery disease						Nocturnal angina
	Not significant	Spasm only	1 vessel	2 vessel	3 vessel	Left main stem stenosis	
Total No of patients	26	1	22	22	30	7	12
No with episodes (%)	5 (19)	1	Ambulatory monitoring 11 (50)		17 (77)	7 (100)	12 (100)
Heart rate at onset of episodes (beats/min)	123 (10)	87 (10)	99 (16)	105 (13)	99 (14)	89 (14)	91 (13)
	Exercise testing						
Exercise duration to ST depression (mm)	9 (2.7) (n=6)	—	5.4 (2.5) (n=13)	5.5 (2.3) (n=16)	3.9 (1.8) (n=22)	2.6 (1.2) (n=6)	2.8 (1.1) (n=10)
Heart rate at 1 mm ST depression (beats/min)	136 (16) (n=6)	—	124 (25) (n=13)	114 (22) (n=16)	109 (19) (n=22)	99 (16) (n=6)	100 (10) (n=10)

—, negative

disease and 15 with frequent ST segment depression shows that the mean heart rate is higher during the morning and early afternoon compared with the evening and is lowest at night (Fig. 3).

#### COMPARISON WITH EXERCISE TESTING

Table 3 shows the mean duration of exercise before significant ST segment depression occurred in patients who had ST segment changes during ambulatory ST segment monitoring. The duration of exercise to significant (1 mm) ST segment depression was shorter in patients with more severe coronary artery disease (left main stem stenosis, nocturnal angina, and three vessel disease) compared with patients with less severe coronary disease. These differences were, however, not statistically significant.

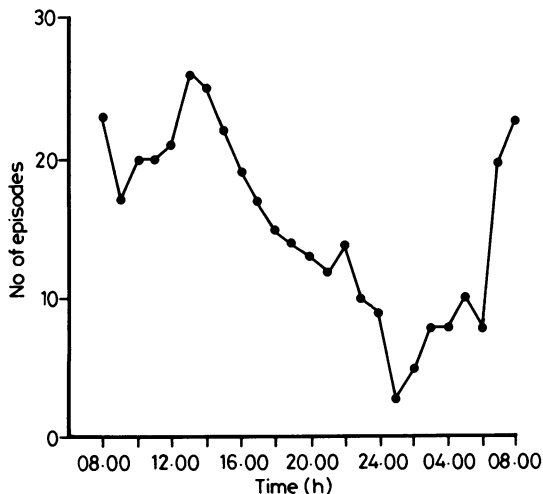


Fig. 2 Diurnal variation in the number of episodes of transient ST segment change in 73 consecutive patients over 24 hours.

The mean heart rate at the time of 1 mm ST segment depression tended to be higher in patients with no significant coronary artery disease (136 beats/min) when compared with patients with coronary artery disease (113 beats/min) (not statistically significant). Patients with relatively severe disease, left main stem stenosis and three vessel disease, had a lower heart rate threshold at which significant ST segment depression occurred during stress testing (Table 3). Patients who had a very low threshold to ST segment depression during the exercise tests had more frequent episodes of ST segment depression, which also lasted longer (Table 4), although the differences were not statistically significant. All 40 patients who developed 1 mm ST segment depression during the first six minutes of exercise had episodes of ST seg-

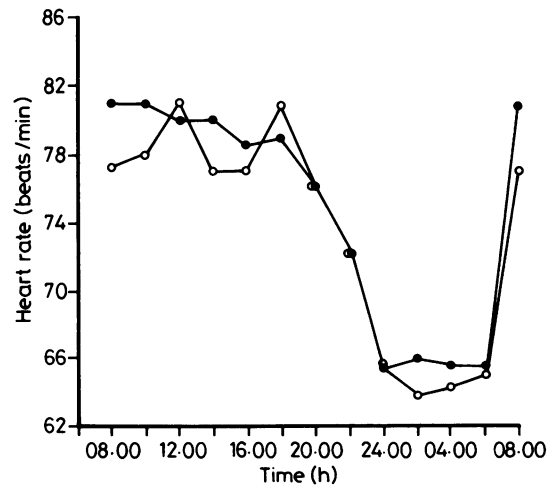


Fig. 3 Diurnal variation in the mean hourly heart rate in 15 patients with normal coronary arteries (○) and 15 patients with frequent angina pectoris (●).

Table 4 Presence, frequency, and duration of ambulatory ST segment changes in patients with coronary artery disease (CAD) and positive exercise tests (1 mm ST segment depression)

No of patients with CAD	20	20	8	2
Duration of exercise to 1 mm ST depression (min)	≤3	4-6	7-9	10-12
No of episodes of ST change	7.6 (8)	2.8 (2.2)	1 (1.3)	0
Duration of episodes (min)	132 (124)	38 (35)	33 (50)	0
No of patients with no ambulatory ST segment changes	0	0	2	2

ment change during ambulatory monitoring. In contrast, four patients with exercise tests becoming positive after nine minutes (stage III of the modified Bruce protocol) had no episodes during ambulatory ST segment monitoring (Table 4).

A majority of patients (86%) with a positive exercise test within three minutes of the modified Bruce protocol had two or three vessel coronary artery disease, but only 35% of patients with such disease had a positive test at this low workload (Table 2). Only seven of the 11 patients with frequent nocturnal ischaemia during ambulatory monitoring had an exercise test which was positive within three minutes and one had a negative exercise test. Whereas all the patients with left main stem stenosis who were exercised had a positive stress test, only four of the six developed significant ST segment depression within the first three minutes of exercise.

## Discussion

Abundant laboratory and clinical evidence now exists to show that shifts in the ST segment on the electrocardiogram in patients with coronary artery disease represent episodes of myocardial ischaemia, whether or not these episodes are associated with pain.<sup>16-18</sup> Changes in the ST segment accompanying myocardial ischaemic events have been recorded under controlled conditions such as at rest or during exercise testing for many years. Ambulatory electrocardiographic ST segment changes have been capable of accurate and reliable recording and reproduction only since the advent of recorders with an adequate low frequency response<sup>15</sup> (0.05 Hz < 3 db down). A few studies have been conducted to detect the occurrence of ST segment changes in patients with chest pain,<sup>7,8,14</sup> those with a positive exercise test,<sup>12,13</sup> and those with varying severity of coronary artery disease.<sup>9,13</sup> Nevertheless, none of these studies included consecutive patients, and the patients studied were highly selected. By studying consecutive admissions we have been able to determine the true incidence of daytime angina, nocturnal rest angina, and coronary artery

spasm with normal coronary arteries in the population of patients referred to one hospital. This has enabled us to determine the implications of the varying frequency and duration of ST segment changes observed during ambulatory monitoring in relation to findings at coronary arteriography and during conventional exercise testing.

The results of monitoring 73 consecutive patients with significant coronary artery disease show that the number and duration of episodes of ST segment change increase with increasing severity of the underlying disease, but there is a substantial overlap between the groups. Myocardial ischaemia occurred more frequently during the daytime than during the evening and night (Fig. 2). The diurnal variation in the averaged hourly heart rate in 15 patients with the most frequent episodes of ST segment changes (Fig. 3) did not differ significantly from that in patients with normal coronary arteries. The close correlation between the basal heart rate changes and the frequency of myocardial ischaemia during the day and at night highlights the importance of underlying changes in metabolic demand in the development of myocardial ischaemia during daily life. This has been confirmed in a recent study comparing atenolol with pindolol in patients with angina pectoris.<sup>19</sup> Suppression of basal heart rate with the former drug reduced the ischaemic episodes significantly when compared with pindolol, which did not reduce basal heart rate as a result of intrinsic sympathomimetic activity.

The importance of heart rate changes at the onset of myocardial ischaemia has also been shown: the mean heart rate before the onset of ST segment depression was (101 (12) beats/min) higher than the basal heart rate during any time of the day or night (Fig. 3). By performing an analysis of momentary changes in the heart rate before the onset of ST segment depression, we have shown that there are invariably small but significant increases in heart rate before the onset of ST segment depression in patients with obstructive coronary artery disease.<sup>20</sup> It must be emphasised that different magnitude of increases in heart rate precede episodes of ST segment change in individual patients and in patients with similar severity of coronary artery disease. Although these findings indicate the importance of changes in metabolic demand in the precipitation of myocardial ischaemia, other possible factors such as increases in end diastolic pressures during recumbency and dynamic coronary stenosis cannot be entirely excluded.

The heart rate threshold before myocardial ischaemia occurred was lower in patients with more severe forms of coronary artery disease during stress testing (Table 3), a finding also reported in previous studies.<sup>21</sup> The heart rate at the onset of the episodes of ST segment change during ambulatory monitoring

was similarly lower in patients with more severe disease such as left main stem stenosis. The mean heart rate at the onset of ST segment depression during ambulatory monitoring was 10–20 beats/min lower than the heart rate at which 1 mm ST segment depression occurred during exercise testing (Table 2). Measurement of the heart rate at the first change in the ST segment during exercise testing has not been performed and is certain to be lower; thus there seems to be a similarity in the mean heart rate threshold to ischaemia in both exercise testing and ambulatory monitoring, although there is often a large variation in individual patients.

Exertional angina is considered to be secondary to myocardial oxygen demand exceeding supply, whereas rest and nocturnal ischaemia is often considered to be secondary to coronary spasm.<sup>22</sup> Ambulatory electrocardiographic ST segment monitoring is unique in being able to identify non-invasively this group of patients with normal coronary arteries and coronary spasm. This is a rare condition and accounted for only one of the 26 patients with normal coronary arteries and one of the 12 patients with nocturnal angina pectoris. The other 11 patients with nocturnal angina had three vessel or left main coronary artery disease and a very low exercise threshold to ischaemia. Thus patients with severe coronary artery disease develop ischaemia even at rest, and coronary spasm in normal or near normal coronary arteries is a relatively rare cause of nocturnal angina.

Both exercise testing and ambulatory monitoring failed accurately to predict patients with normal coronary arteries. Six patients with no significant coronary artery disease had episodes of ST segment changes during ambulatory monitoring. Five of these patients also had false positive exercise tests. The other patient was shown to have coronary spasm induced at angiography but had a negative exercise test. The duration of exercise to ST segment depression and the heart rate at which ST segment depression occurred (136 (16) beats/min, range 120–155 beats/min) was much greater in patients with normal coronary arteries than in those with significant coronary artery disease (Table 3). Similarly, the heart rate at which ST segment depression occurred during ambulatory monitoring in these five patients (123 (10) beats/min, range 108–137 beats/min) also tended to be higher than in patients with significant coronary disease. False positive exercise tests with similar episodes of ST segment depression during ambulatory monitoring have been previously reported in young healthy volunteers.<sup>23</sup> The heart rate at which ST segment depression occurred in these healthy subjects was 135 (20) beats/min (range 100–180 beats/min), a rate similar to that of patients in this series with normal or near normal coronary arteries. Thus patients with normal

coronary arteries developed ST depression at relatively high heart rates during both ambulatory monitoring and exercise testing.

Attempts have been made in the past to correlate the electrocardiographic changes during exercise testing with the long term prognosis in patients with ischaemic heart disease.<sup>24</sup> The patients with ST segment depression at low workload, those with a greater magnitude of ST segment depression, and those with exercise induced ventricular arrhythmias have a worse prognosis and also tend to have more severe forms of coronary artery disease. Information on the prognostic importance of ambulatory electrocardiographic ST segment changes is lacking. Nevertheless, it is widely known that patients with three vessel disease and left main stem coronary artery disease have a relatively poor long term prognosis. It would, therefore, be valuable to identify non-invasively this subgroup in a group presenting with chest pain. These results show that ambulatory ST segment monitoring detected transient episodes of ST segment changes in 80% of the patients with three vessel disease and in all patients with left main stem stenosis. Patients with more severe coronary artery disease also had more frequent episodes of ST segment changes during the day (Table 1). Indeed 11 of the 12 patients with nocturnal angina had either severe two or three vessel disease or left main stem stenosis. Exercise tests were also positive in 79% of the patients with three vessel disease, but the duration of exercise did not identify patients who had nocturnal ischaemia nor those with left main stenosis (Table 2). Mortality and morbidity in patients with three vessel coronary artery disease varies,<sup>25</sup> and those patients who have more frequent ischaemia may possibly have greater risk of infarction or death, although long term studies are required to substantiate this view.

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