Transient myocardial ischaemia after acute myocardial infarction

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Abstract

The prevalence and characteristics of transient myocardial ischaemia were studied in 203 patients with recent acute myocardial infarction by both early (6.4 days) and late (38 days) ambulatory monitoring of the ST segment. Transient ST segment depression was much commoner during late (32% patients) than early (14%) monitoring. Most transient ischaemia (>85% episodes) was silent and 80% of patients had only silent episodes. During late monitoring painful ST depression was accompanied by greater ST depression and tended to occur at a higher heart rate. Late transient ischaemia showed a diurnal distribution, occurred at a higher initial heart rate, and was more often accompanied by a further increase in heart rate than early ischaemia.

Thus in the first 2 months after myocardial infarction transient ischaemia became increasingly common and more closely associated with increased myocardial oxygen demand. Because transient ischaemic episodes during early and late ambulatory monitoring have dissimilar characteristics they may also have different pathophysiology and prognostic implications.

Current evidence suggests that important coronary artery disease frequently remains silent until the onset of a severe morbid clinical event. Thus myocardial infarction is often not preceded by angina¹ and more than 50% of patients resuscitated from out of hospital ventricular fibrillation deny previous cardiac symptoms despite angiographically demonstrated clinically significant coronary artery stenoses.² Recent attempts to identify and assess coronary disease have therefore focused on ways of detecting silent myocardial ischaemia as well as symptomatic episodes. Ambulatory ST segment monitoring is increasingly being used for this purpose because it is now widely accepted that any transient ST segment depression recorded reflects true myocardial ischaemia in patients with proven coronary artery disease.³⁻⁵

Much is currently known about the frequency, characteristics, and significance of silent myocardial ischaemia during ambulatory monitoring in patients with both stable⁶ and unstable angina⁷ but there is little

information on patients with acute myocardial infarction. We therefore performed repeated ambulatory monitoring in 203 patients with recent acute myocardial infarction and we report the frequency and characteristics of transient myocardial ischaemia in this population.

Patients and methods

All patients admitted to the Royal Liverpool Hospital (September 1987 to December 1988) with definite acute myocardial infarction⁸ were considered eligible for the study unless they were in Killip class D, had significant valve disease, left ventricular hypertrophy, electrocardiographic conduction defects, other serious diseases, or were currently taking digitalis. Of 358 patients screened 14 refused consent, 24 died shortly after admission, and eight patients had been recruited previously. A further 109 patients were excluded because of the criteria listed above. We therefore performed ambulatory monitoring in 203 patients (152 men and 51 women, mean age 58 years (range 34-76)) with myocardial infarction.

The infarct was anterior/lateral in 93 (46%) patients, inferior/posterior in 110 (54%), non-Q wave in 47 (23%), and 36 patients (18%) were treated by thrombolysis. Forty six patients (23%) had a previous myocardial infarction, 74 (36%) had at least a 1 month history of angina pectoris, 23 (11%) were diabetic, and 114 (56%) were current smokers.

AMBULATORY ST SEGMENT MONITORING

Single channel ST segment monitoring was performed with the Oxford Medilog 4000-II. Previous studies⁹ including those in our laboratory (unpublished) showed that this real time ambulatory monitoring equipment reliably measured ST segment shift both at rest and on exercise. The single modified V5 lead (CM5) predominantly used in this study was highly sensitive for detecting exercise induced myocardial ischaemia and only rarely did a second simultaneous inferior lead detect the maximum ST change.^{10 11}

Ambulatory recordings were made both early (before discharge) and late (4-8 weeks after admission). Recording periods were limited to 24 hours because longer periods—for example 48 hours—are more impractical and expensive and we found only occasionally detected ischaemia not apparent on a 24 hour recording. Pre-gelled electrodes (Deva Medical) were applied and skin impedance

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Table 1 Procedural details of ambulatory ST segment monitoring after myocardial infarction

Details	Ambulatory monitoring		p
	Early (6.4 days) (%)	Late (38 days) (%)	
Total patients	201	177	
Lead position:			
Modified V5	185 (92)	150 (85)	
Modified V6	7 (3)	12 (7)	
CC5	4 (2)	5 (3)	
Others	5 (2)	10 (6)	
Recording ECG lead:			
Q wave present	31 (15)	15 (8)	<0.04
Baseline ST elevation	38 (19)	8 (5)	<0.001
Baseline ST depression	44 (22)	19 (11)	<0.004
Drug treatment taken during monitoring			
β Blocker	71 (35)	28 (16)	<0.001
Nitrate	41 (20)	33 (19)	
Calcium antagonist	19 (9)	17 (10)	
At least one drug	102 (51)	63 (36)	<0.004

was checked (Oxford Medical Systems XI-1) to ensure a reading of less than 5 k Ω . Before each recording, patients adopted the supine, right lateral, prone, left lateral, and standing positions and underwent a period of hyperventilation (each manoeuvre for 30 seconds). ST segment shift with posture was taken into account in the analysis (see below).

Patients were given a diary to record the times of onset and finish of symptoms and daily activities and were interviewed after monitoring to ensure that all symptoms had been recorded and any discrepancies in the diaries were corrected.

ST SEGMENT ANALYSIS

The magnetic tapes (TDK AD60 cassettes) were replayed (Oxford 4500 system) to produce a report of the ST segment and heart rate trends. The ST level while the patient was supine was usually chosen as the baseline; however, if there was ≥ -0.5 mm (-0.05 mV) additional ST depression from the supine level during any postural manoeuvre then the maximum ST depression during such manoeuvres was used as the baseline. Episodes of ST depression were identified on the ST trend and validated by examining, with X8 magnifying lens and a 0.1 mm graticule, electrocardiogram strips printed at each point of interest. Transient myocardial ischaemia was defined as ≥ 30 s of at least -1.0 mm planar/downsloping ST depression, measured at 80 ms after the J point.¹² If there was baseline ST depression of

≥ -0.5 mm, then further (-1.0 mm) ST depression had to be present before ischaemia was diagnosed. Episodes of ST depression were considered to be separate if the ST shift was absent for at least 3 consecutive minutes. ST segment elevation was not used in this analysis to diagnose transient ischaemia because the diagnostic specificity of this change on ambulatory monitoring has not been well established.

The presence or absence of a significant increase in heart rate (arbitrarily chosen as ≥ 10 beats/min and resembling the figure set by other workers³) above the adjacent baseline in association with each episode of ST depression was determined by examining the computer derived heart rate trend. The heart rate at the onset of significant ST depression and the time of onset, associated symptoms, and daily activities during such episode were noted. Daily activities were classified as mental (for example, reading or watching television), physical (for example walking, washing, dressing, housework), exertional (for example shopping and climbing stairs or hills), resting, and sleep.

STATISTICAL ANALYSIS

We compared differences in prevalence of early and late ST depression and episodes of myocardial ischaemia associated with increased heart rate by a χ^2 test. We used the standard error of the difference between the two means to compare the heart rates at the onset of early and late ST depression and the Wilcoxon rank sum test to compare the characteristics of silent and symptomatic ischaemic episodes.

Early and late ambulatory monitoring periods were compared directly in a subgroup of patients who were taking identical medication during both recordings. The diurnal pattern of ischaemia was analysed in patients taking no antianginal drugs during ambulatory monitoring.

ETHICAL CONSIDERATIONS

The study was approved by the local ethics committee and all patients gave informed consent.

Results

BACKGROUND INFORMATION

Early ambulatory monitoring (mean 6.4 days, range 3–15) was performed in 201 patients (99%) and late recordings (38 days, range 22–93) were obtained in 177 patients (87%). Recording lasted a mean (SD) of 23.1 (2.6) and 23.5 (1.0) hours/patient respectively. Table 1 gives further details. Q waves or baseline ST segment deviation in the recording lead and concurrent β blockade were commoner during early monitoring.

TRANSIENT MYOCARDIAL ISCHAEMIA

While transient ST depression developed on late ambulatory monitoring in one third of patients, only one in seven had such changes on

Table 2 Prevalence and characteristics of transient ST depression

Variable	Ambulatory monitoring		p
	Early n (%)	Late n (%)	
Patients with STD	29/201 (14)	56/177 (32)	<0.001
STD duration (min)	1102	2731	
Total STD episodes	107	280	
STD with HR increase	40/107 (37)	211/280 (75)	<0.001
HR at STD onset (mean (SD))	82 (15)	99 (20)	<0.001
Proportion silent STD	91/107 (85)	264/280 (94)	
Symptoms in patients with STD:			
All STD episodes silent	24/29 (83)	48/56 (86)	
STD sometimes symptomatic	3/29 (10)	5/56 (9)	
STD always with angina	2/29 (7)	3/56 (5)	

HR, heart rate (beats/min); STD, transient ST segment depression.

Figure 1 (A) Diurnal variation of early transient myocardial ischaemic episodes (—▲—) in patients (n = 201) undergoing ambulatory monitoring 6-4 days after acute myocardial infarction compared with episodes in patients (n = 99) taking no antianginal drugs (—△—). (B) Diurnal variation of late transient ischaemia (—●—) in patients (n = 177) undergoing ambulatory monitoring 38 days after myocardial infarction compared with episodes in patients (n = 114) taking no antianginal drugs (—○—).

early (pre-discharge) monitoring (table 2). Later episodes occurred at a higher (+25%) heart rate at onset and were much more commonly associated with periods of increased heart rate (≥ 10 beats/min increase) than early ST depression. These differences between early and late ischaemic episodes were also apparent in a subgroup (101 patients) taking identical antianginal drugs during both their early and late ambulatory monitoring (see later).

The pattern of late transient ischaemia showed diurnal variation with ST depression predominating during the waking hours while the pattern of early transient ischaemia was more random—though early episodes seemed to be more common in the late afternoon and evening (fig 1). Early transient myocardial ischaemia showed little diurnal change in distribution in 99 patients who were not taking antianginal drugs during early monitoring (fig 1).

Transient ischaemia was overwhelmingly asymptomatic (table 2). In fact, >80% of patients with either early or late ST depression showed only silent episodes; a further 10% of patients had both silent and symptomatic

episodes and the remaining 10% experienced angina during all episodes of ST depression. The presence of absence of symptoms had no effect on the characteristics of early ST depression but during late monitoring symptomatic ST depression was greater ($p < 0.0001$) than the silent change in the ST segment (-1.8 (0.14) v -1.3 (0.02) mm, mean (SEM)) and tended to occur at a higher heart rate (105.8 (6.9) v 98.1 (1.2) beats/min, $p = 0.13$). The duration of symptomatic and silent ST depression did not differ significantly (11.5 (4.8) v 9.7 (0.9) min, $p = 0.6$).

During early monitoring most (64%) episodes of ST depression occurred at rest or during sleep, 33% during low level physical or mental activities, and only 2% during exertion (table 3). During later recordings, however, most (57%) of ST change occurred at times of low level physical or mental daily activity, 39% at rest or in sleep, and very little (5%) was related to exertion (table 3).

The maximum ST depression detected during episodes of early or late transient ischaemia (fig 2) was rarely more than -2.0 mm; however, a small number of episodes of ST change greater than -3.0 mm were recorded. Most episodes of ST depression detected on early or late monitoring lasted less than 10 minutes (81/107 episodes (76%) and 200/280 (71%) respectively) but 2-3% of episodes lasted >1 hour (maximum duration 107.5 minutes during early monitoring and 134 minutes during late monitoring).

EFFECT OF DRUG TREATMENT ON TRANSIENT ISCHAEMIA

We identified a subgroup of 101 patients who were on identical treatment during both their early and late ambulatory recordings (table 4). Two thirds (67%) of these patients were not taking antianginal drugs, 25% were on single agents, and 9% were taking a combination of treatments during the two recording periods. The characteristics of transient ischaemia in this subgroup resembled those of the study population as a whole—ST depression was more frequent during late recordings than during early recordings, there were significantly more episodes of ST depression related to an increase in heart rate during late monitoring than during early monitoring, and the mean heart rate at the onset of ST depression during late monitoring was also greater (table 4).

Furthermore, in this drug matched group, only 6 of the 12 patients with early ST depression developed any ST changes during late monitoring while 27 (82%) of the 33 patients with late ST segment depression did not show any ST shift during early monitoring.

The diurnal pattern of transient ischaemia was also examined in those patients not taking antianginal drugs during ambulatory monitoring (99 patients during early monitoring and 114 during late monitoring). Early and late monitoring in these subgroups detected 49 and 204 ischaemic episodes respectively. The diurnal distributions of these ischaemic episodes, uninfluenced by drug treatment, were similar to that of the whole study population (fig 1).

Table 3 Daily activities during episodes of transient myocardial ischaemia

Activity	Ambulatory monitoring	
	Early n (%)	Late n (%)
Period of rest	47 (52)	71 (27)
Walking	13 (14)	54 (21)
Low-level physical activity	5 (6)	52 (20)
Mental activity	12 (13)	42 (16)
Sleeping	11 (12)	31 (12)
Exertion	2 (2)	13 (5)
Total episodes	90*	263*

*The associated activity was unknown in 17 early and 17 late episodes of ST depression.

Figure 2 (A) Maximum ST depression (1 mm = 0.1 mV) during episodes of early transient myocardial ischaemia in patients (n = 201) undergoing ambulatory monitoring 6.4 days after myocardial infarction. (B) Maximum ST depression during transient ischaemia detected in patients (n = 177) undergoing ambulatory monitoring 38 days after myocardial infarction.

The relatively small number (49) of episodes of ST depression during early monitoring means that interpretation of the data remains uncertain.

Seventy one patients were taking β blockers during early ambulatory monitoring; in six late monitoring was not performed and 48 stopped taking the drug during late monitoring. In this latter group transient ST depression was commoner ($p < 0.04$) during late monitoring than during early monitoring (16/48 patients (33%) *v* 7/48 (15%)). In 17/71 patients who were taking β blockers during both recordings transient ST depression was equally common early and late (three and two patients).

INFLUENCE OF INFARCT CATEGORY, THROMBOLYTIC TREATMENT, AND DIABETES MELLITUS

The prevalence of transient myocardial ischaemia during both early and late monitoring was independent of infarct site or the presence of Q waves and was not increased in diabetic patients or in patients treated by thrombolysis.

Table 4 Ambulatory ST segment monitoring in patients taking identical treatments during early and late recordings

Details	Ambulatory monitoring		p
	Early n (%)	Late n (%)	
Total patients	101	101	
Treatment during monitoring:			
Single drug	25 (25)	25 (25)	
β Blocker	10 (10)	10 (10)	
Nitrate	13 (13)	13 (13)	
Calcium antagonist	2 (2)	2 (2)	
Combined drug treatment	9 (9)	9 (9)	
Two drugs	8 (8)	8 (8)	
Three drugs	1 (1)	1 (1)	
No drug treatment	67 (67)	67 (67)	
Patients with STD	12/101 (12)	33/101 (33)	0.001
Duration of STD (min)	434	1639	
Total STD episodes	40	161	
Proportion of silent STD	33/40 (83)	155/161 (96)	0.005
STD with HR increase	17/40 (43)	108/161 (67)	0.005
HR at STD onset (mean (SD))	85 (13)	100 (21)	0.001

HR, heart rate in beats/min; STD, transient ST depression.

Discussion

Silent myocardial ischaemia can cause ventricular arrhythmias,¹³ sudden death,² or myocardial infarction¹⁴ and may lead to cumulative impairment of left ventricular function.¹⁵

Recently the prevalence of silent ischaemia has been studied by ambulatory monitoring in various subgroups with coronary disease^{6,16,17}; patients with recent acute myocardial infarction, however, have received little attention. Bigger *et al* detected ischaemic ST segment changes in 28% of 50 patients during ambulatory monitoring at 3 months after myocardial infarction; surprisingly, none of these episodes was symptomatic.¹⁸ During pre-discharge ambulatory monitoring in 103 patients with myocardial infarction Gottlieb *et al* also detected ischaemic ST segment changes in 30 patients (29%)—mostly silent—and this group experienced a threefold increase in mortality at one year.¹⁹ The study patients were a highly selected population, however, in whom left ventricular ejection fraction was $< 40\%$.

In the largely unselected group of patients in this study transient ST depression was present during both early and late ambulatory monitoring—though it was considerably more frequent later (33% *v* 12%). This difference probably largely reflects greater patient activity and hence greater myocardial oxygen demand during the later phase of recovery from myocardial infarction; and indeed many episodes (46%) of ST depression during late recordings were associated with some degree of physical activity whereas on the predischage tapes 77% of such episodes occurred without any accompanying physical exertion. Some of the difference may, however, be artefactual in that the high prevalence of pre-existing and unresolved baseline ST shift (either elevation or depression) in the monitoring lead during early recordings (table 1) may have masked further significant ST depression. The timing of ambulatory monitoring after myocardial infarction may therefore be crucial. If the recording is made too early, the sensitivity of the test may be poor but if the detection of silent ischaemia after myocardial infarction is to be of prognostic value and to have a beneficial influence on treatment then monitoring cannot be delayed too long, because a high proportion of cardiac events occur in the early weeks after infarction.²⁰ Nearly all (90%) transient ischaemic episodes detected both in this study and in that of Bigger *et al*¹⁸ were silent and indeed in 80% of patients showing ST depression all episodes were symptomless. Thus a greater proportion of ischaemic episodes are silent in patients shortly after myocardial infarction than in other subgroups with coronary artery disease. Although silent and painful episodes were similar in many respects, painful episodes were associated with a significantly greater degree of ST depression on recordings at 4–8 weeks after infarction.

We found a distinct pattern of diurnal variation in the incidence of transient ischaemia late after myocardial infarction which resembled that seen by others,^{6,21} with most episodes occurring in the morning. This circadian cycle is likely to be related both to the known

variation of plasma catecholamines²² with corresponding changes in vasomotor tone²³ and the variation of heart rate and blood pressure²⁴ with accompanying increases in myocardial oxygen demand.

Interestingly ST depression on early monitoring showed little circadian variation (fig 1). The explanation of this feature is not clear but it may reflect an equalisation of myocardial oxygen demand during convalescence in hospital or possibly a loss early after infarction of diurnal variation in substances affecting coronary supply. Increased prescription of β blockers during early ambulatory monitoring may be partly responsible because others have shown a similar circadian distribution (with a tendency to afternoon and evening ischaemia) in patients with angina on drug treatment.²⁵ Even so, during early monitoring we did not see a morning predominance of early transient ischaemia even in patients who were not taking drugs.

In this study very few ischaemic episodes occurred during physical exertions that were vigorous enough to increase myocardial oxygen demand and cause ischaemia. This suggests that coexisting changes in coronary arterial supply may be having an effect. Perhaps at times of high coronary tone—for example in the mornings, even small increases in myocardial oxygen demand may cause ischaemia whereas the same increase in demand when coronary tone is lower may produce no ischaemia. The incidence of ischaemia as well as its temporal distribution may thus depend on the interplay between factors affecting both myocardial oxygen supply and demand. Furthermore, since early transient ST depression occurred at a lower heart rate and with less frequent increase in heart rate than that on later recordings (table 4), a reduced coronary supply early after myocardial infarction may be of greater pathophysiological importance than late changes.

The reduced occurrence of transient ST depression in patients in whom treatment with β blockers continued during late ambulatory monitoring suggests that increased myocardial oxygen demand may be important in the pathophysiology of late transient myocardial ischaemia and offers a possible explanation for the known benefits of β blockers after myocardial infarction—abolition of silent transient ischaemia.

What was the effect of concurrent drug treatment on the prevalence and characteristics of ST segment change? More patients were taking antianginal medication (especially β blockers) on early monitoring. None the less, the frequency and characteristics of early and late transient ischaemia in a subgroup taking identical treatment during both recordings (table 4) were similar to those of the population as a whole, and the overall diurnal pattern of ischaemia (fig 1) resembled that seen in patients not having drug treatment; but the number of patients studied was too small for a definite conclusion to be reached.

Our study showed that predominantly silent transient ischaemia was detected by ambulatory ST segment monitoring in a high proportion of patients shortly after acute

myocardial infarction and defined its characteristics. The relation of this transient ischaemia to exercise induced ischaemia, left ventricular function, ventricular arrhythmias, and prognosis is being studied further.

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