Natural variability of transient myocardial ischaemia during daily life: an obstacle when assessing efficacy of anti-ischaemic agents?

D J Patel, D Mulcahy, J Norrie, C Wright, D Clarke, I Ford, K M Fox

Abstract

***Objective*—To assess the degree of variability of transient myocardial ischaemia during daily life in patients with coronary artery disease, which could confound the interpretation of trials of the therapeutic effects of anti-ischaemic agents.**

***Design*—Prospective method evaluation.**

***Setting*—Tertiary referral centre, outpatient clinic.**

***Patients*—Patients with stable angina, confirmed coronary artery disease, and a positive treadmill exercise test for ischaemia. Patients were not preselected on the basis of prior documented transient ischaemia during ambulatory ST segment monitoring.**

***Interventions*—A simulated drug-study with 4 monitoring phases in 16 subjects. To minimise variability in ischaemic activity, patients underwent weekly 48 hour ambulatory ST segment monitoring outside hospital off all prophylactic therapy on the same weekdays for 4 weeks.**

***Main outcome measure*—Variability in the frequency and duration of transient myocardial ischaemia.**

***Results*—There was marked variability in both ischaemic activity and mean duration of ischaemia in patients with confirmed ischaemia, the greatest degree of variability being between patients and from day to day within weeks within patients, with a further contribution to variability being noted between fortnights within patients.**

***Conclusions*—Despite assessment off all therapy and an adequate period of monitoring (48 hours) with small intervals between monitoring periods (5 days), marked variability in ischaemic activity was noted, and regression towards the mean was clearly shown. Ambulatory ST segment monitoring outside hospital is not a reliable method for assessing the therapeutic effects of anti-ischaemic agents.**

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Keywords: stable angina; transient myocardial ischaemia; ST segment monitoring; drug trial design

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The use of ambulatory ST segment monitoring has made it possible to assess the characteristics of transient ischaemic activity during daily life in patients with coronary artery disease. Many patients with stable angina have predominantly asymptomatic (and sometimes frequent) ischaemic episodes during their daily activities.[1–3] It has been reported that there is a significant natural variability in such ischaemic activity,[4–6] not only between but within patients.[5 6] Ambulatory ST segment monitoring is increasingly being used to assess the anti-ischaemic effects of various therapeutic agents or interventions. Natural variability in ischaemic activity, if it were marked, could result in either under-estimation or overestimation of a therapeutic effect. Various groups have recommended that at least 48 hours of continuous ambulatory ST segment monitoring should be performed to minimise such an effect,[4–6] and in addition have noted that, when there are multiple monitoring periods (such as in a therapeutic study), the shorter the interval between monitoring periods, the less likely is variability in ischaemic activity.[6]

In a prospective study, we performed serial weekly 48 hour periods of ambulatory ST segment monitoring in patients with stable angina off therapy as though it were a short-term randomised drug study, in order to investigate the degree of variability in ischaemic activity when the length of, and intervals between monitoring periods were designed to minimise such effect.

Patients and methods

We studied 16 men (mean age 58 years (range 36–73 years)) with coronary artery disease (eight, single vessel; three, two vessel; five, three vessel disease), stable angina on standard medical treatment, and a positive exercise test for both ischaemia and angina within nine minutes using the Bruce protocol. All had had angina for at least five months (range 5–120 months) before inclusion. Ten had a previous history of myocardial infarction. One patient had undergone coronary artery bypass surgery but symptoms had recurred, and three others had undergone coronary angioplasty but had developed recurrent angina in association with documented angiographic restenosis.

All patients were studied each week for 4 weeks. Each patient underwent 48 hours of ambulatory ST segment monitoring outside hospital while off routine anginal treatment for at least five half-lives before monitoring started and during the monitoring periods (patients took short acting diltiazem three times a day for three days from the end of each monitoring period). Ambulatory monitoring was performed on the same days of each week for each patient. Patients were not preselected on the basis of

prior documented transient ischaemia during ambulatory ST segment monitoring.

Standard exclusion criteria included inability to stop routine medications, the presence of significant conduction defects, or the taking of medications likely to effect interpretation of the ST segment. The study was approved by the ethics committee of the Royal Brompton Hospital.

AMBULATORY ST SEGMENT MONITORING

All patients underwent 48 hours of ambulatory ST segment monitoring on the same weekdays each week for four weeks off all routine antianginal treatment, and outside hospital. Monitoring was performed with pre-gelled electrodes to record two bipolar leads, the anterior lead CM5, and a modified inferior lead. Sites and methods of application have been previously described.[2] Two channel recordings were then obtained on magnetic tape using a frequency modulated dual channel recorder (Oxford Medilog MR35), and tapes were analysed at 60–120 times normal speed using the Oxford Medilog MA20 scanner. All printouts were at 25 mm/s. Significant ST segment depression was defined as planar or downsloping shift of the ST segment of $\geqslant 1$ mm measured 0·08 s after the J point that persisted for more than one minute. Changes in the T wave vector were not regarded as evidence of myocardial ischaemia unless they were accompanied by significant ST segment changes. We recorded the frequency and duration of each ischaemic episode in addition to the heart rate one minute before, and at the onset of each episode.

During each period of ambulatory ST segment monitoring, patients were encouraged not only to continue with their normal daily activities but also to attempt to avoid widely diversified activities from one monitoring day to the next. Each 48 hour monitoring period was performed on the same days of each week in an attempt to minimise variation in activity level related to specific days—that is, active working days *v* leisurely weekends.

STATISTICAL ANALYSIS

The main response of interest was the number of ischaemic episodes recorded in 48 hours of ambulatory monitoring, comprising two consecutive 24 hour periods. All subjects had complete and analysable tapes available for all occasions. In addition the total duration of ischaemia and the mean heart rates at onset of ischaemia were recorded for each 48 hour period. These data were tabulated to permit study of the variability between patients and then within patients and the variability among weeks in the 48 hour readings and between 24 hour tapes within weeks.

Sample size calculations for a parallel group design were based on the use of an approximate two-sample t test. Such a test might commonly be used in practice although the data being studied could not be claimed to arise from a normal distribution. Performance of the two-sample t test was assessed and sample sizes were calculated using a simulation study based on a more realistic model for the data. The counts for each subject were assumed to follow a Poisson distribution with the mean of each subject varying as a gamma random variable. The parameters used for these distributions were estimated from the data collected in the study. The power of a study to detect a treatment effect of a given magnitude was calculated for a variety of sample sizes, and the sample sizes required to give a study of given power then calculated by interpolation.

Sources of variability in both the transformed count and transformed duration of episodes were separated using a nested analysis of variance with days (a 24 hour tape) nested within week, within fortnight, and within patient. The natural logarithm of the duration of episodes was used and the count of episodes was transformed to $\log_e$ (count +1) to try to lessen the violation of the assumptions of the analysis: that is, to make the data less skewed (more "normal") and stabilise the variance across the time periods of interest.

Results

A total of 2990 hours of ambulatory ST segment monitoring (128 24 h periods; mean 187 hr/patient) was available for analysis, during which time 142 episodes of transient ischaemia (87 (61%) asymptomatic) were recorded in 11 patients. The frequencies of transient ischaemic episodes on a day by day and on a weekly basis are shown in figs 1 and 2. Five patients had no

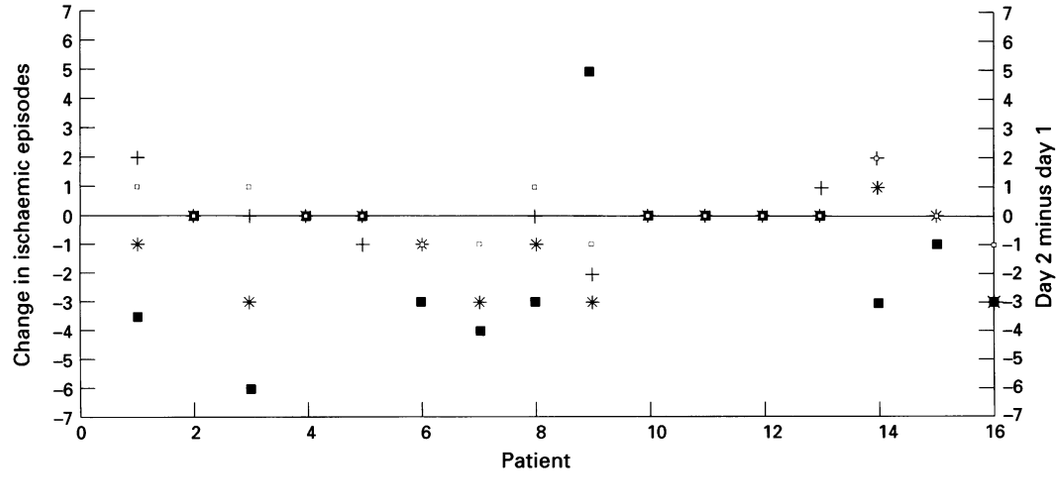

Figure 1 Change in frequency of episodes of transient myocardial ischaemia per 24 hours between second and first 24 hour tape (day 2 − day 1).

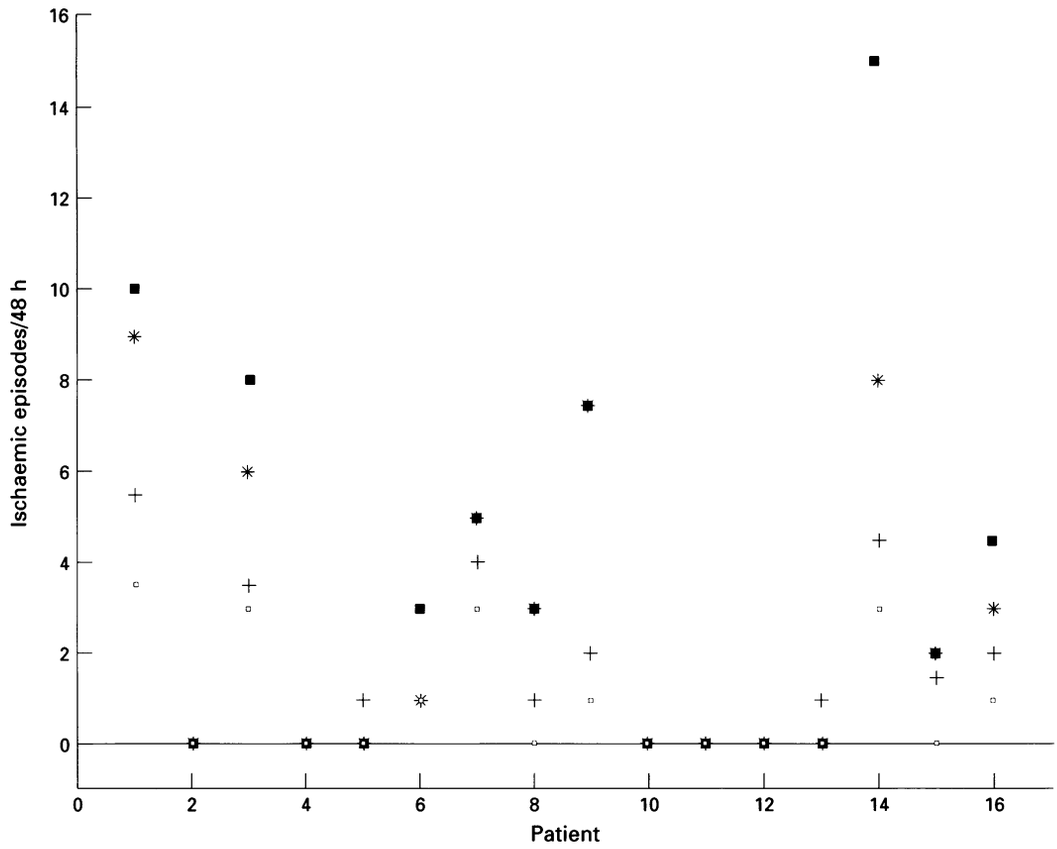

Figure 2 Week by week frequency of episodes of transient myocardial ischaemia per 48 hours in all patients.

ischaemic episodes during any period of monitoring despite reporting continued anginal symptoms. Seven of the 16 study patients (43%) had *at least* one ischaemic episode during *every* period of monitoring. The log mean duration of ischaemic episodes is shown on a weekly basis in fig 3. Both duration and frequency of episodes show substantial variability, and this variability increases as each of these quantities increases in magnitude, demonstrating that there is marked within as well as between patient variability in ischaemic activity on a week by week basis in patients with stable angina. Figure 4 shows that there is also within and between patient variability in heart rate at onset of ischaemia,

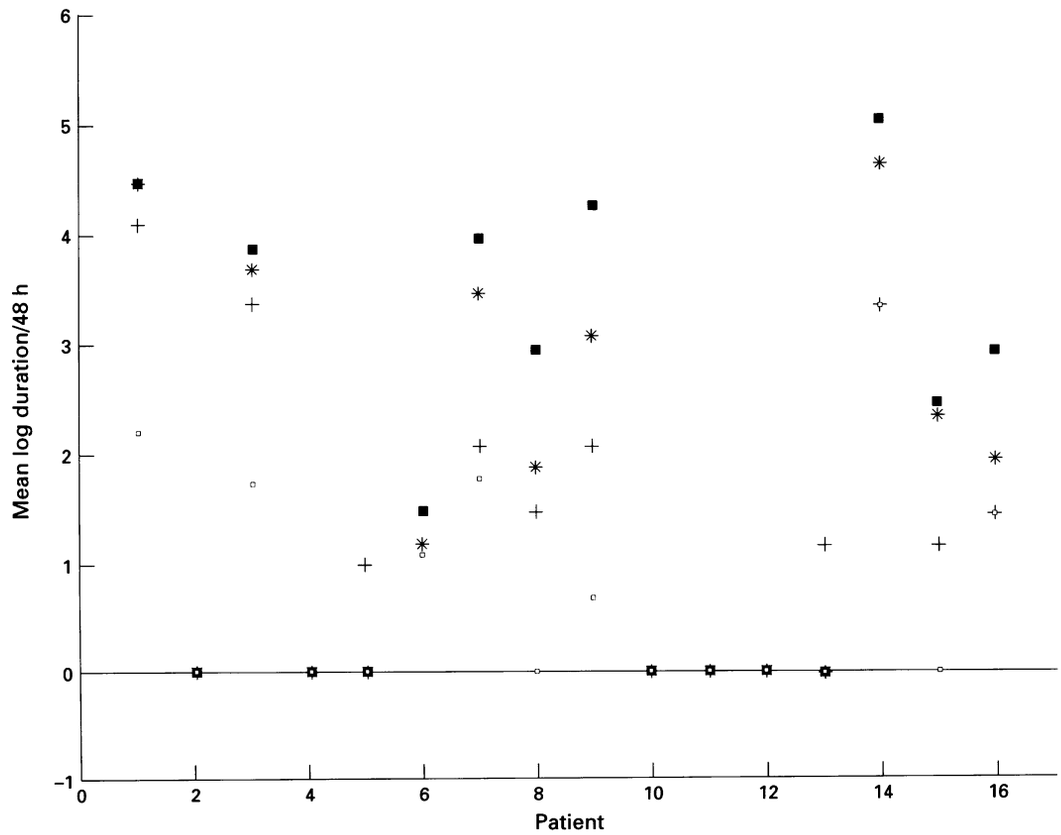

Figure 3 Week by week variability in the mean log duration (minutes) of ischaemia per 48 hours for all patients.

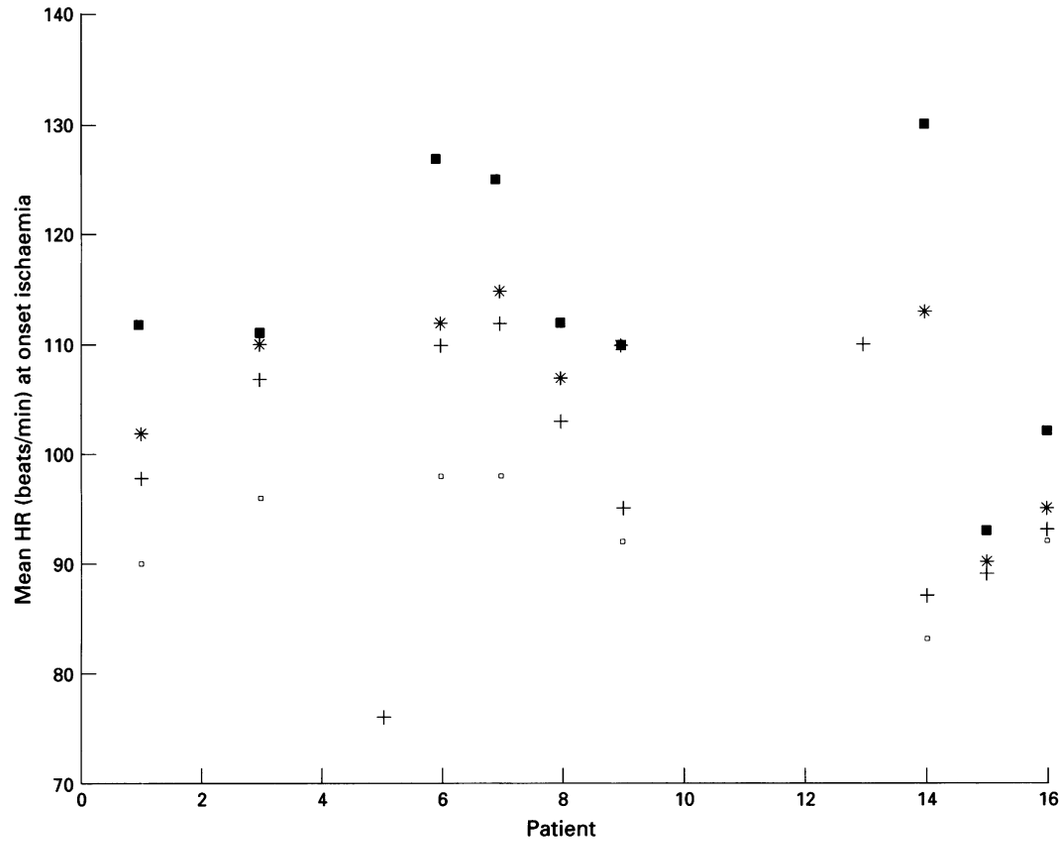

Figure 4 Week by week variability of mean heart rate at onset of ischaemia for patients with transient ischaemic episodes.

suggesting a varying ischaemic threshold. Almost 80% of all ischaemic episodes, however, were preceded by an increase in heart rate of more than 5 beats/min in the minute before onset of ischaemia.

Nested analysis of variance showed that most of the witnessed variability was accounted for by variability between patients and on a day to day basis within patients (table 1). There was no evidence of additional variability among weeks within fortnights; however, there was a significant additional component of variability between fortnights within patients. This would be consistent with an association between the time between measurements and the variability in measured ischaemia, and with the assumption that a period of one week between measurements is not sufficient time to detect a difference in a study of this size.

To illustrate regression towards the mean of ischaemic episodes from one recording period to the next we chose at least one, two, three, four, or more ischaemic episodes per 48 hours as "baseline". With at least four ischaemic episodes required for inclusion, nine of 11 (82%) suitable monitoring periods were followed by reduction in ischaemic activity, compared with none in which ischaemic activity increased during the next monitoring period (table 2). In those periods with two or more ischaemic episodes per 48 hours, 13 (62%) of 21 such monitoring periods were followed by a reduction in ischaemic activity, compared with five (24%) that were followed by an increase in ischaemic activity over the next 48 hour period.

Table 1 Sources of variability of transient myocardial ischaemia

Source of variation	*Frequency*	*Duration*
Between patients	0·22 (46)***	1·93 (52)***
Between fortnights within patients	0·05 (10)*	0·67 (7)*
Between weeks within fortnights within patients	0·00 (0)	0·00 (0)
Between days within weeks within patients	0·22 (45)	1·56 (42)

Sources of variability for the transformed frequency of transient ischaemic episodes and the log of their duration between patients, between fortnights within patients, between weeks within fortnights, and between days within weeks. Each source is given as the estimated variance component, and in parentheses as a percentage of the total variability ***P < 0·001; *P < 0·05.

Table 2 Regression towards the mean

	Initial number of ischaemic episodes per 48h			
	> 1 (n = 28)	*> 2 (n = 21)*	*> 3 (n = 17)*	*> 4 (n = 11)*
In the next 48 hours monitoring there were:				
Fewer ischaemic episodes	16 (57)	13 (62)	11 (65)	9 (82)
More ischaemic episodes	6 (21)	5 (24)	3 (18)	0 (0)
No change	6 (21)	4 (19)	3 (18)	2 (18)

Illustration of regression towards the mean for various screening strategies (selecting two or more, three or more, four or more, five or more ischaemic episodes per 48 hours monitoring as inclusion criteria). Number of adjacent by time measurements greater than, less than or the same as each other (figures in parentheses are percentages).

Table 3 Predicted sample sizes

Power (%)	*Treatment effect (% reduction)*	*No of subjects per group*
80	20	600
	25	400
	30	260
90	20	720
	25	520
	30	360

Estimated total number of subjects required for a two-treatment parallel group design study (single 48 hour period of observation for each treatment group) for different combinations of power and treatment effect for a nominal level of significance of 5%.

Discussion

There is little doubt that ambulatory ST segment monitoring has been extremely useful as a research tool in investigating the activity of ischaemia in various populations with coronary artery disease, and particularly in assessing the frequency and characteristics of silent myocardial ischaemia. This investigative method has become increasingly popular as a method of assessing the effects of various therapeutic agents on transient ischaemic activity during daily life, despite the contradictory findings about the prognostic significance of transient ischaemia in stable angina.[7-10]

Unlike formal exercise testing, however, where the procedure is supervised to ensure that patients achieve predefined haemodynamic and symptomatic end points, ambulatory ST segment monitoring is performed outside hospital, and any findings are to a large extent influenced by the patient's day by day and moment by moment chosen activities and environmental stresses, resulting in continually changing demands on the myocardium, and, in patients with significant coronary artery disease, a variable propensity to ischaemia. This alone is likely to influence significantly the observed natural variability of ischaemia reported during daily life. It is unlikely that rigid standardisation of activities from day to day would be complied with, were this attempted in an effort to reduce variability, and indeed such an approach would render relatively meaningless the concept of "during normal daily activities".

This study confirms an important degree of variability in ischaemic activity within patients (and also between patients), both on a day by day basis and on a week by week basis, even though, for each patient, all studies were performed on the same days of each week. The variability in heart rate at onset of ischaemia supports the assumption that alterations in the determinants of myocardial oxygen demand are not the only mechanism at play in the genesis of ischaemic episodes during daily life. This variation in ischaemic threshold may further contribute to variation in ischaemic activity. It has been recently reported that there is a circadian variation in ischaemic threshold, with ischaemia occurring at lower heart rates at night and in the early morning, which implies a higher basal coronary tone at these times.[11] It is likely the between patient variability is at least partly influenced by the differing severity of coronary artery disease, as well as by differing activity patterns.

Various studies have addressed the issue of variability in ischaemic activity in ambulant coronary patients. Khurmi and Raftery[12] performed 24 h periods of monitoring on two occasions, six weeks apart in patients with stable angina off therapy, and reported that ambulatory ST segment depression was reproducible. They concluded that this technique could prove to be a valuable method of assessing the effects of anti-anginal drugs. Tzivoni *et al*[4] performed 72 h of continuous monitoring on 20 patients with stable angina, and suggested that, whereas 24 h of recording was sufficient for "clinical" purposes, 48 h of recording is required for assessment of therapeutic drug efficacy in view of significant day to day variability in ischaemic activity. Nabel *et al*[5] studied 42 patients with stable angina off therapy, performing 48 hours of ambulatory ST segment monitoring at baseline and then at weekly and/or monthly intervals. They reported that there was considerable variability in ischaemic activity, and that the power to detect a designated reduction in frequency and duration of ischaemic episodes increases as the monitoring period lengthens from 24 to 48 h, and as the time interval between monitoring periods shortens. They recommended at least 48 h of monitoring to minimise variability. Celermajer and coworkers[6] performed serial periods of ambulatory monitoring in 36 patients with stable angina, who had between four and 28 total days of monitoring off therapy. In assessing the components of ischaemic variability, they noted that the greatest sources were between patients and between days within patients for all end points. While they noted an additional source of variability between weeks, they reported no additional variability between months.

Whereas most investigators have used short periods of ambulatory monitoring (usually between 24 and 48 h) to identify ambulatory ischaemia for characterisation or prognostic purposes, the issue of variability becomes particularly important when one tries to assess the effects of a therapeutic agent(s) on such ischaemic activity: is it the drug or natural variability that has apparently altered the ischaemic profile? The practical clinical relevance of this question relates to the design of studies which incorporate such a method of assessment, and to the use of serial monitoring to assess therapeutic effect in the clinical setting. From the variability in ischaemic activity demonstrated in this small prospectively designed study, certain statistical assessments can be made as how best to perform meaningful studies which use ambulatory ST segment monitoring to assess the effects of therapeutic agents on ischaemic activity. Table 3 shows the approximate sample sizes required for specified powers and percentage reduction for nominal size of 5 %, assuming a parallel group design (those for the 20% reduction should be viewed with caution as they are extrapolations and not interpolations). When one considers the observation by Nabel *et al*[5] that variability will decrease with shorter intervals between monitoring, it is noteworthy that in the present study there were only five monitoring-free days between assessment periods: it is probable that in most studies where the therapeutic effect is being assessed, the periods between monitoring will be significantly greater (usually between 12 and 26 days), and consequently the problem of variability may be greater. The present study confirms this observation, showing a greater variability in ischaemic activity between fortnightly monitoring periods than between weekly monitoring periods, however, most of the witnessed overall variability in ischaemic activity is

explained by the day to day variability within each 48 hour monitoring period.

One of the difficulties relating to ambulatory ST segment monitoring is its relative insensitivity in detecting ischaemia when compared with exercise testing.[8-10 13] This problem can be overcome by preselecting patients with transient ischaemia on a screening recording (it usually requires screening of 2–3 patients to find one suitable patient). Over 25% of patients in this study had no transient ischaemic activity detected over 192 hours of recording despite being off anti-anginal therapy and having confirmed coronary artery disease and a positive exercise ECG for both ischaemia and angina at less than nine minutes of the Bruce protocol. The study of patients with frequent ischaemia may represent the best compromise of the use of this technique; however, the present work suggests that day to day variability becomes even more marked as the frequency of ischaemia increases. When patients are selected on the basis of having a predefined number of ischaemic episodes, then regression towards the mean[14] will be observed (as demonstrated herein), resulting in exaggeration of any therapeutic effects documented. This effect will become more marked as the number of ischaemic episodes required for inclusion in studies becomes greater. Also patients with frequent daily ischaemia tend to have more severe coronary disease[1 15] and an ischaemic response at low work loads.[1 2 13] They may not be ideal candidates for drug withdrawal, and may undergo early revascularisation procedures on clinical grounds, thus being potentially unrepresentative of the overall population of stable angina patients for whom the drug treatment under study is being evaluated. If a consistent and predefined frequency of ischaemic activity over two 48 h monitoring periods were required for a patient to be included in therapeutic studies, it would become extremely difficult to identify suitable patients, as shown by our findings and confirmed in recent large studies,[16 17] where over 45% of patients on placebo (second monitoring period) after randomisation had significant reduction or abolition of ischaemia compared with baseline.

This prospective study demonstrates many of the practical difficulties with using serial ambulatory ST segment monitoring for the assessment of anti-ischaemic agents. Despite adequate monitoring periods and minimal intervals between monitoring periods, there was considerable day to day variability in ischaemic activity within patients, which primarily accounted for the marked week by week variability and that between patients. A likely contributor to such natural variability is simple variability in activity levels from patient to patient and from day to day within patients, as is the case during normal daily life outside hospital. In practical terms this problem is very difficult to correct as so many influences on ischaemia abound, ranging from temperature, shopping, working, eating, going out, emotional factors, resting, and sleep. This issue underscores the potential importance of standardisation of conditions when assessing treatment effect. Can agent A be accurately compared with agent B in terms of its 24 hour anti-ischaemic effect, when the patient went dancing while taking agent A and stayed in because of the cold weather while taking agent B?

Based on the findings of this study and on previous reports, either large numbers of patients should be investigated or sufficient ischaemic episodes be present in order to have a reasonable power to detect the magnitude of differences likely to be achieved with anti-ischaemic agents in studies, allowing for the problems alluded to above. Because there is considerable between patient variability, cross-over study designs are likely to require fewer patients than parallel group designs. It is probable, however, that variability will remain a problem as long as patients perform different activities from day to day. This study shows that, in the clinical setting, serial ambulatory monitoring is not a suitable investigative approach for accurate assessment of response to therapeutic manoeuvres.

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