Variability of Transient Myocardial Ischemia in Ambulatory Patients With Coronary Artery Disease

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Ambulatory electrocardiographic (ECG) monitoring of patients with chronic stable angina has demonstrated frequent and prolonged episodes of ischemic ST segment depression, but its clinical use requires an understanding of the components and extent of variability. Therefore, variations in the frequency and duration of episodes of ST segment depression were evaluated with ambulatory ECG recording at daily, weekly, and monthly intervals in 42 patients with chronic stable angina and known coronary artery disease. Data were analyzed with a nested analysis of variance design that yields estimates of variance components. From the estimates of variance components, power calculations and minimum significant percent reductions in frequency and duration of ischemia were derived. During 4,656 hours of ambulatory ECG monitoring, 1,262 episodes of ischemic ST segment depression were detected. The frequency of episodes was 6.3 ± 0.45/24 hr (mean ± SEM), and the duration of episodes was 18.3 ± 2.8/24 hr. Because of variability over time, the ability to detect significant changes was dependent upon the number of subjects, length of monitoring period, and intervals between monitoring periods. In a clinical trial, for example, a sample size of 25 patients monitored for 48 hours with 1 week between control and test conditions would require a 65% reduction in frequency, whereas a sample size of 50 patients monitored under similar conditions would require a 46% reduction in frequency, to attribute the change with 90% power to a therapeutic intervention rather than to a spontaneous variation. When monitoring a single patient for 48 hours with 1 week or 1 month between control and repeat monitoring sessions, episodes of ischemic ST depression must be eliminated to detect significant therapeutic changes in ischemic activity at the 95% confidence level. Therefore, an understanding of the variability of episodes of ischemic ST segment depression on ambulatory ECG monitoring permits the rational design of clinical trials and individual assessment in patients with active ischemic heart disease. (Circulation 1988;78:60–67)

Appearance of transient myocardial ischemia is an important functional expression of coronary artery disease. Clinical studies using the exercise tolerance test, thallium scintigraphy, and gated blood pool studies of regional left ventricular function have shown that the presence and severity of ischemia mediate risk and affect prognosis in patients with coronary artery disease.1–3 These tests are informative, especially when the patient is asymptomatic.4 Ambulatory electrocardiographic (ECG) monitoring of ischemia in patients with coronary artery disease has demonstrated that many patients have episodes of symptomatic ST segment depression and much more frequent asymptomatic events during daily activities, and these episodes have been shown by imaging studies to reflect reversible myocardial ischemia.5–8 The characteristics of ischemic episodes of ST segment depression have been well defined in patients with stable coronary artery disease, and ambulatory ECG monitoring now provides an opportunity to quantify ischemic events in an individual patient or in groups of patients over time to assess significant changes in disease activity. However, it is necessary to understand the naturally occurring fluctuations in isch-
emia and the sources of variability that occur in a patient population with chronic stable angina.

The purpose of this study was to systematically examine the sources of variability affecting the frequency and duration of episodes of ischemic ST segment depression in a population of patients with stable angina and documented coronary artery disease. These procedures allow the calculation of the minimum detectable changes in ischemic frequency and duration that are required to detect significant alterations in disease activity. This study should provide a secure basis for measuring important increases or decreases in ischemic activity outside of the hospital that may be useful in the management of patients and in the evaluation of new therapies.

Patients and Methods

One hundred ten consecutive patients with chronic stable angina pectoris, positive exercise tolerance tests, and angiographically documented coronary artery disease underwent 48 hours of ambulatory ECG monitoring from January 1985 to September 1986 at the Brigham and Women’s Hospital, Boston, Massachusetts. Patients who met the following eligibility criteria were included in the analysis: 1) evidence of at least one episode of ST segment depression (defined as ≥0.1 mV planar or downsloping ST segment depression persisting 0.08 seconds beyond the J point and lasting for >30 seconds) during the initial 48-hour period; 2) withdrawal of antianginal medication 48 hours before and during the entire study with use of sublingual nitroglycerin as needed; 3) absence of atrial fibrillation, significant valvular disease, and electrocardiographic signs of conduction defects and left ventricular hypertrophy; and 4) absence of medications, such as digoxin, that could alter the ECG. Forty patients had no episodes of ST segment depression on initial monitoring, and 28 patients were monitored on antianginal therapy; these 68 patients were excluded from analysis. Forty-two patients met eligibility criteria, and they formed the patient population for this study. In addition to the initial 48-hour monitoring period, patients were monitored again at weekly and monthly intervals.

During the study period, all patients had chronic stable angina pectoris. No patient developed unstable angina or required hospitalization for myocardial infarction, cardiac catheterization, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery. Written, informed consent was obtained in accordance with guidelines established by the Committee for the Protection of Human Subjects at the Brigham and Women’s Hospital.

Ambulatory Monitoring

ECG recordings were made with a calibrated Oxford Medilog II frequency-modulated recorder (Bedford, Massachusetts) with two bipolar leads attached to exploring electrodes. Electrode placement was determined from the two most positive leads on exercise testing. The frequency-modulated recorder was calibrated with standard 1-mV signals. Patients were instructed to carry out their usual daily activities, except for bathing. A structured diary was used to record activity, symptoms, and use of sublingual nitroglycerin.

The tapes were analyzed visually at 60 or 120 times real time with an Oxford Medilog MA 20 scanner. Calibration and baseline ECG tracings were printed for reference use. Each episode of ST segment depression that met the following criteria was printed: when planar or downsloping ST depression of 0.1 mV or greater (compared with baseline) persisted 0.08 seconds beyond the J point, and when changes were present in consecutive beats for more than 30 seconds. The duration of the episode was defined as the total number of minutes of 0.1 mV or greater ST segment depression. A separate, additional episode was recorded when the ECG returned to baseline for at least 3 minutes. All tapes were manually read by two independent, experienced readers. The results were reviewed together or by a third independent reader. Only those episodes with mutual agreement between two readers were included for analysis. The following features were recorded for each episode: time of onset and offset, duration of the episode (minutes), presence...

**FIGURE 1.** Histograms of distribution of frequency (Panel A) and average duration (Panel B) of ischemic episodes per 24 hours in 42 patients. Mean frequency per 24 hours of 42 patients was 6.3±0.45 episodes. Average duration of episodes per 24 hours across 42 patients was 18.3±2.8 minutes.
or absence of symptoms, use of nitroglycerin, and heart rate at the onset of the episode.

Data and Statistical Analysis

For each patient, the frequency of episodes, total duration of episodes, average duration of episodes, number of symptomatic episodes, and average heart rate at onset of episodes were determined for each 24-hour period. Results are expressed as the mean ± SEM.

The data from the 42 patients yielded 194 monitoring periods such that 84 represented pairs of consecutive 24-hour periods (48 hours total). Allowing for varying follow-up in the different patients, 40 of the 194 monitoring periods represented follow-up monitoring at a 1-week interval, and 70 represented longer-term follow-up sessions at monthly intervals. No patient contributed more than 10 data points, and 20 patients had some follow-up at weekly or monthly intervals. These data were analyzed by means of a nested analysis of variance design in which the following factors served as random effects: patients, months within patients, weeks within months within patients, and days within weeks within months within patients. The analysis used each of the following measures in turn as the dependent variable: frequency of episodes, average duration of episodes, total duration of episodes, and average heart rate at onset of episodes. The design yielded estimates of the variance components associated with each of the factors listed above. Variance associated with consecutive 24-hour periods could not be estimated separately from error variance in this design; thus, the percentage of variance attributed to the “between-days” effect reported below is synonymous with the random measurement error usually reported in linear models. Further analyses consisted of power calculations based on the estimates of variance components described above. These calculations were performed in two ways. First, in the dependent measures listed above, the percentages of daily or weekly change that could be detected with 90% power and 5% one-sided type I error were determined with sample sizes of 15, 25, and 50 patients. Second, power curves for a sample size of 20 patients, presuming 5% one-sided type I error and a 50% reduction in the dependent measures, were produced. The percent reductions were calculated relative to the mean value of each respective dependent measure.

Results

Patient Characteristics

The patient population consisted of 33 men and 9 women, aged 60.2 ± 1.5 years (range, 36–81 years). Fourteen patients (33.3%) were classified as New York Heart Association (NYHA) Class I; 19 patients (45.3%) were classified as Class II; eight patients (19%) were classified as Class III; and one patient (2.4%) was classified as Class IV. Four patients were asymptomatic, and each had a positive exercise tolerance test and coronary angiogram demonstrating coronary artery disease. All study patients had exercise tolerance tests diagnostic for coronary artery disease on a standard Bruce protocol. Twenty-two patients (52%) had a history of at least one previous myocardial infarction, and all of these patients experienced recurrent symptoms with a positive exercise tolerance test. Thirty-four patients (81%) underwent coronary angiography: five (14.7%) had one-vessel disease; 13 (38.2%) had two-vessel disease; and 16 (47.1%) had three-vessel disease. Six patients (14%) underwent coronary artery bypass graft surgery before enrollment in the study, but each patient developed recurrent angina and had a positive exercise tolerance test before enrollment in the study.

Ambulatory Monitoring

The 42 patients underwent 4,656 hours (194 24-hour periods) of ambulatory ECG monitoring, and 1,262 episodes of ischemic ST segment depression were recorded. This accounted for a total duration of 218 hours and 20 minutes of ischemic activity. A distribution of the frequency and mean duration of
ischemic ST segment depression in the first 24 hours for each of the 42 patients is demonstrated in Figure 1. The mean frequency of episodes per 24 hours across all observations of the 42 patients was 6.3 ± 0.45 episodes. The mean duration of episodes across all observations ranged from 0 to 454 minutes with a mean of 18.3 ± 2.8 minutes. The mean total duration of episodes across all observations was 55.2 ± 7.1 minutes. The mean heart rate at the onset of an ischemic episode was 101 ± 1.4 beats/min (range, 67–148 beats/min). Seventy-seven of the 1,262 ischemic episodes (6%) were associated with anginal symptoms as measured by entry in a patient diary.

Components of Variability

The variance components by source (between patients, between months, between weeks, and between days) are listed in Table 1 for the frequency, mean duration, total duration, and heart rate at onset of ischemia per 24-hour monitoring session. The major variations in frequency of ST segment depression occurred both between patients and between weeks. In the other three variables, the variation between patients was the sole major source, accounting for more than half of the total variation in the other three variables.

Variation in Groups of Patients

The variance components in frequency and duration of ischemia were calculated for groups of patients to determine the minimum percent change required to demonstrate statistically significant reductions in ischemic frequency and duration between a control and test period when evaluating, for example, the effects of drug therapy. Table 2 and Figure 2 illustrate several possible protocols of different sample sizes with 24- and 48-hour monitoring periods 1 day and 1 week apart. With a sample size of 15 patients, for example, the minimum percent reduction in frequency of ischemic episodes during a test period required to attribute with 90% power, an effect due to the intervention rather than spontaneous variation, would be 50% if patients were monitored for 24 hours at 1-day intervals and would be 91% if patients were monitored for 24 hours at 1-week intervals. If the length of monitoring were increased to 48 hours, then the average number of ischemic episodes per 24-hour period could be observed for each patient, where the average is calculated across the two 24-hour periods. Because such averages are less variable than a single observation, a minimum percent reduction in frequency

<table>
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<tr>
<th>Sample size</th>
<th>Length of monitoring (hr)</th>
<th>Length of interval (between control and test)</th>
<th>Reduction in ischemic episodes (minimum %)</th>
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FIGURE 2. Plot of percent reductions required in frequency of ischemia to detect a significant change with 95% confidence when monitoring for 24- and 48-hour periods at 1-day and 1-week intervals. With increasing numbers of patients, smaller percent reductions are required to demonstrate an effect attributable to therapy, rather than to spontaneous variation.
of only 35% would be required if control and test conditions occurred 1 day apart and 84% if monitoring were performed 1 week apart. By increasing the sample size of patients, the minimum percent reductions in frequency and mean duration required to demonstrate significance at the 95% confidence level are reduced. For example, with a sample size of 50 patients, reductions in frequency of 19% and 46% would be required if monitoring occurred for 48 hours at 1-day and 1-week intervals, respectively. Calculations for minimum reduction in frequency and mean duration of ST segment depression in sample sizes between 5 and 50 patients for a variety of monitoring periods are shown in Figure 2. The percent reductions are calculated relative to the population means and can be converted to absolute change by multiplying by the appropriate means. For example, a 50% drop in frequency corresponds to an absolute drop of 0.5 × 6.3 = 3.15 ischemic episodes since the average number of ischemic episodes was found to be 6.3.

To determine the probability of detecting significant percent reductions in frequency and mean duration of ischemic episodes in a group of patients, power probability curves were derived for a sample size of 20 patients monitored for 24–48 hours at 1-day and 1-week intervals (Figure 3). As the monitoring period is increased from 24 to 48 hours and as the time interval between control and test conditions is shortened from 1 week to 1 day, the power to detect significant changes in disease activity increases. For example, the power to detect a 50% reduction in frequency when monitoring for 24-hour periods at 1-week intervals is 0.58. However, if monitoring occurred for 48 hours with 1 day between control and test conditions, the power to detect a 50% reduction in frequency would be 0.99.

Likewise, if the goal of an intervention was to produce a 50% reduction in frequency and duration of ST segment depression, then power calculations can be derived from Table 1 for various sample sizes to detect statistical significance. The power to detect a reduction in frequency or mean duration increases as the sample size of patients increases and as the time between control and test periods shortens. For example, the power to detect a 50% reduction in frequency with a sample size of 10 patients monitored 1 week apart is 0.37. Increasing the sample size to 25 patients increases the power probability to 0.66 when monitoring 1 week apart and 0.98 when monitoring 1 day apart.

**Individual Variation**

Within a single patient, there is variation in the frequency and mean duration of ischemia over days, weeks, and months of ambulatory monitoring despite a lack of change in a patient’s symptoms. An illustrative example of monitoring for 48 hours at intervals of several weeks and months in an individual patient is presented in Figure 4. Even though the patient’s clinical status and exercise tolerance test results remained stable throughout the 9-month monitoring period, ECG ambulatory monitoring demonstrated marked fluctuations in the frequency and duration of ischemia.

With direct estimation of day-to-day variability, as well as the previous variance components, the variability in frequency and duration of ischemia for a single patient over a designated monitoring period was calculated. The variability between monitoring
periods in a single patient is large, given the range of changes in frequency and mean duration of ischemia that occur spontaneously. In general, Figure 5 demonstrates that the power to detect a designated reduction in frequency and average duration of episodes increases as the monitoring period lengthens from 24 to 48 hours and the time interval between monitoring periods shortens.

Additional calculations show that to detect with 90% power, a reduction in ischemic activity at the 95% confidence level (two-sided), the number of episodes of ischemic ST depression must drop by 15.2 when monitoring a single patient for 24 hours with 1 week or 1 month between repeat monitoring sessions. Likewise, when monitoring a single patient for 48 hours with 1 week or 1 month between sessions, a decrease of 10.6 episodes/day or of 79 min/24 hr would be a significant change in ischemic activity at the 95% confidence level not attributable to spontaneous variation.

Discussion

This study has quantified the variability of frequency and duration of episodes of ischemic ST segment depression at regular intervals in a population of patients with stable angina pectoris and coronary artery disease. The results demonstrate that variability in the frequency and duration of ischemic episodes increases over time. An analysis of the sources of variability reveals that variation between patients is considerable, suggesting that each patient is his own control when assessing response to therapy.

When evaluating ischemic activity in a single patient, either as a baseline measure or as a serial change over time, the extent of intraindividual variability demands at least 48 hours of monitoring. Similar principles apply when monitoring episodes of ischemic ST segment depression within groups of patients in clinical trials, except that the number of patients in each study group also determines the minimum detectable change that can be measured with confidence. For example, if 50 patients undergo 48 hours of monitoring 1 week apart, then a 46% change in frequency of episodes can be detected with 90% power at the 95% confidence. This information is necessary when trying to identify important improvements or worsening of ischemic activity that could be spontaneous or could be the result of a new therapy in a clinical trial.

Episodes of ST Segment Depression as Markers of Ischemia

An examination of ECG recorders and playback units has shown that an adequate frequency response (less than 3 dB down at 0.05 Hz) and minimum phase shift are required to accurately record ischemic-type ST segment depression.9 Frequency-modulated devices appear to be satisfactory, and a variety of clinical observations have supported the notion that episodes of significant ST segment depres-

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from such patients were retained. These maneuvers corrected the skewed distribution. Both of these re-analyses yielded results similar to those of the original analyses. Thus, although the departure from normally distributed data suggests that the estimates presented here should be interpreted with caution, it does not appear that serious distortions are present. The results of this paper can be used in designing future intervention studies. However, the results of those studies should be analyzed, if possible, with methods that avoid normality assumptions.

Clinical Implications of Transient Myocardial Ischemia

For years, exercise tolerance test studies in symptomatic and asymptomatic populations have shown that a positive exercise tolerance test and the severity of ischemia are both related to an adverse prognosis and an increased risk of coronary events. The Multiple Risk Factor Intervention Trial and Lipid Research Clinics Mortality Follow-up Study both emphasize the relation between exercise-induced ischemia and an adverse prognosis. Interestingly, the majority of these positive results were in people with asymptomatic ischemia, and the data did not include a knowledge of the coronary anatomy. Conversely, patients with known coronary artery disease but no inducible ischemia have shown an excellent outcome and a very low risk of coronary events. Recent studies have demonstrated that patients with left main or three-vessel coronary artery disease and inducible ischemia on exercise testing benefit from coronary artery bypass graft surgery. Prospective studies have shown that myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease similarly affects prognosis. This strengthens the need to understand the variability of transient myocardial ischemia when trying to assess prognosis and treatment in individuals and in groups.

Clinical Use of Ambulatory Monitoring

The application of ambulatory ECG monitoring implies that the clinician intends to follow the progress and response to treatment in individuals and in groups of patients during their normal daily activities. Therefore, this study has examined the sources of variability and demonstrated that 48 hours of monitoring is probably the minimum required to permit identification of a significant change in ischemic activity with confidence while following the progress in any individual. The majority of these stable patients had between 0 and 8 episodes of ischemia each day, and the data show that in a single patient, all episodes should be eliminated to be confident of improvement. There is good evidence that this is possible, and eliminating these episodes may become a desirable goal if ischemia affects prognosis. Significant improvement can be detected with smaller changes when more than one patient or a group of individuals is

**Figure 5.** Plots of power probability to detect percent reductions in the frequency (Panel A) and duration (Panel B) of ischemic episodes in a single patient. Monitoring for 48 hours at 1-day intervals is optimal to detect changes in ischemic activity.
studied, and a clinical trial with 50 patients will enable identification of a 46% change with 95% confidence. Variability of ischemic activity and, therefore, significant improvement and worsening can be quantified and controlled in patients with stable angina pectoris. This provides a firm basis for using this measure of potentially harmful ischemia when trying to control ischemic damage in patients with coronary artery disease.

References

Key Words • ambulatory electrocardiographic monitoring • angina • myocardial ischemia
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