Observer Variability and Optimal Criteria of Transient Ischemia During ST Monitoring with Continuous 12-lead ECG

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Background: ST monitoring with continuous 12-lead ECG is a well-established method in patients with unstable coronary artery disease (CAD). However, the method lacks documentation on optimal criteria for episodes of transient ischemia and on observer variability.

Methods: Observer variability was evaluated in 24-hour recordings from 100 patients with unstable CAD with monitoring in the coronary care unit. Influence on ST changes by variations in body position were evaluated by monitoring 50 patients in different body positions. Different criteria of transient ischemia and their predictive importance were evaluated in 630 patients with unstable CAD who underwent 12 hours of monitoring and thereafter were followed for 1 to 13 months. Two sets of criteria were tested: (1) ST deviation ≥ 0.1 mV for at least 1 minute, and (2) ST depression ≥ 0.05 mV or elevation ≥ 0.1 mV for at least 1 minute.

Results: When the first set of criteria were used, the interobserver agreement was good ($\kappa = 0.72$) and 8 (16%) had significant ST changes in at least one body position. Out of 100 patients with symptoms suggestive of unstable CAD and such ischemia, 24 (24%) had a cardiac event during follow-up. When the second set of criteria were used, the interobserver agreement was poor ($\kappa = 0.32$) and 21 (42%) had significant ST changes in at least one body position. Patients fulfilling the second but not the first set of criteria did not have a higher risk of cardiac event than those without transient ischemia (5.3 vs 4.3%).

Conclusions: During 12-lead ECG monitoring, transient ischemic episodes should be defined as ST deviations ≥ 0.1 mV for at least 1 minute, based on a low observer variability, minor problems with postural ST changes and an important predictive value.

A.N.E. 2002;7(3):181-190

electrocardiography; ST monitoring; unstable angina; myocardial infarction; observer variability;
body position

ST-segment monitoring with continuous 12-lead ECG is now a well-established method in patients with acute coronary syndromes (ACS). The method has been shown useful in identifying reperfusion and improved clinical outcome after thrombolysis of patients with ST elevations.^{1,2} In patients with unstable coronary artery disease (CAD), i.e., unstable angina or evolving myocardial infarction (MI) without ST elevation, the method has been shown

to improve detection of transient ischemia and the early risk stratification.^{3,4}

At present, there is no generally accepted standard to define ST episodes during continuous 12-lead ECG monitoring. Based on experiences from Holter recordings,^{5,6} most studies evaluating patients with unstable CAD have used a transient ST change of at least 0.1 mV to define transient ischemia also at 12-lead monitoring.^{3,4} However, in the

The study was supported by grants from the Swedish Heart and Lung Foundation and the Uppsala County Association Against Heart and Lung Diseases, Sweden, and GE Marquette Medical Systems, Milwaukee, Wisconsin, USA.

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Table 1. Clinical Characteristics of the Study Populations

Baseline Variables	Set A (n = 100)	Set B (n = 50)	Set C (n = 630)
Age, median (25 th –75 th percentile), years	67 (59–74)	68 (56–75)	70 (58–77)
Male	70 (70)	36 (72)	375 (60)
Diabetes mellitus	15 (15)		112 (18)
Hypertension	31 (31)		247 (39)
Current smoker	24 (24)		107 (17)
Previous myocardial infarction	31 (31)		195 (31)
Previous revascularisation	19 (19)		103 (16)
ECG on admission†			
Normal ECG	27 (27)	14 (28)	206 (33)
Pathological Q-waves + no ST-T changes	2 (2)	2 (4)	28 (4)
ST-segment depression	11 (11)	1 (2)	77 (12)
ST-segment depression + T-wave inversions	25 (25)	8 (16)	112 (18)
Isolated T-wave inversions	23 (23)	11 (22)	109 (17)
Left ventricular hypertrophy	11 (11)	11 (22)	74 (12)
ST-segment elevation	1 (1)	2 (4)	0 (0)
Other pathological ECG††	0 (0)	1 (2)	24 (4)

If not stated otherwise, the values shown are number of patients and percentages of the group. † In set B ECG was obtained with the patient in supine position, before monitoring. †† Other pathological ECG includes nonsinus rhythm, tachycardia (> 100 beats/minute), left anterior hemiblock and right bundle branch block.

12-lead ECG at rest, presence of even smaller ST depressions will have a predictive value.^{7,8} So far there is a lack of documentation on the influence of different criteria on observer variability, incidence of ischemic and nonischemic ST changes, and the prognostic value.

The purpose of the present study was therefore twofold: (1) to determine the inter- and intraobserver variability of the method when used in patients with unstable CAD, and (2) to elucidate optimal criteria for transient ischemia, with respect to observer variability, postural changes, and prognostic value.

METHODS

Patients

Three sets of patients were included in this study: Set A: Inter- and intraobserver variability was investigated in 100 patients with acute myocardial ischemia verified by ECG (ST depression $\geq$ 0.10 mV or T-wave inversion $\geq$ 0.10 mV) or by raised biochemical markers included in the FRISC II trial.^{9,10} All patients had at least 18 hours of interpretable trend data during the 24 hours of monitoring. Set B: Influence on ST changes of alterations in body position was evaluated in 50 patients admitted to the CCU due to chest pain and suspicion of acute myocardial ischemia. The patients had to be clinically stable with no signs of

ongoing ischemia before inclusion. Set C: The predictive value of different criteria of transient ischemic episodes was elucidated in 630 consecutive patients admitted due to chest pain or other symptoms suggestive of an acute coronary syndrome and without ST elevations on admission ECG.⁴ At least 9 out of the 12 hours of monitoring had to be fully interpretable. Patients with entry 12-lead ECG at rest not interpretable for ischemia, i.e., left bundle branch block, pacemaker treatment, or ventricular rhythm were excluded from all evaluation. Baseline characteristics and ECG findings on admission (set A and C) or in supine position (set B) are listed in Table 1.

ST-Segment Monitoring

Continuous 12-lead ECG was performed using the ST-Guard system (GE Medical Systems, Information Technologies, Milwaukee, WI, USA). This system continuously collects data from all 12 leads, and calculates median QRS-T complexes from the last 10 seconds of monitoring each minute. From these QRS-T complexes an ST trend for each lead is constructed, stored, and displayed on-line.

Skin-electrode impedance was minimized by thorough skin preparation. Monitoring compatible torso limb-lead positions were used according to Krucoff,¹¹ i.e., lateral extent of clavicles and iliac crests in the midaxillary line. ST-segment monitor-

ing with continuous 12-lead ECG was performed from admission and for 24 hours in set A and for 12 hours in set C. Patients were at rest in bed during the monitoring period. In set B, patients were monitored in the following positions: (1) supine (used as a reference), (2) left lateral, (3) right lateral, (4) recumbent in a 45° angle, and finally (5) upright 90° position. For each body position, the patients were monitored at least 2 minutes and until at least two almost identical ECGs with no artefacts had been obtained.

Central Analysis of ST Monitoring

The ST trends were stored on floppy disks and analyzed centrally by a well-trained physician (TJ). For evaluation of intraobserver variability, set A was reanalyzed by the same observer more than 1 year after the first analysis. Interobserver variability was investigated by evaluation of set A also by a research nurse (JC), well trained in interpreting standard 12-lead ECGs but with a limited training of 4 weeks to interpret ST trends from continuous 12-lead ECG. All analyses were done without knowledge of any clinical data or previous judgments of the same recordings.

If the first acquired ECG showed no ST depressions or elevations, this was used as the reference ECG. Otherwise, an ECG as close as possible to normal, at a time point as soon as possible after admission was chosen. An ST episode was defined as a transient ST depression or elevation in any lead, lasting for at least 1 minute (i.e., two consecutive median ECGs). ST depression due to isolated T-wave inversion with unchanged J point was not considered as an ST episode. Concerning the degree of ST deviation, two different criteria were used: Criterion 1: ST depression or elevation ≥ 0.1 mV compared to the reference ECG. Criterion 2: ST depression ≥ 0.05 mV or ST elevation ≥ 0.10 mV compared to the reference ECG. The duration was only measured for episodes fulfilling criterion 1. Episodes had to be separated by at least 1 minute to be regarded as two separate episodes. In order to reduce the effect of heart rate, ST-segment changes were measured at J point + $(1/16 \times \text{R-R interval})$, corresponding to J point + 60 ms at a heart rate of 62.5 beats/min. The leads were grouped into anterior (V^1 - V^4 , I), inferior (II, III, avF) and lateral (avL , V^5 - V^6) leads.

Follow-up

Patients in set C were followed for a median time of 6 months (range 1-13 months). The recorded predefined end points were cardiac death, and the composite of cardiac death or MI. All in-hospital events were registered in the local database of the Swedish Register of Cardiac Intensive Care.¹² Only new MIs occurring more than 24 hours after admission were considered as new events. Out of hospital, information about death and cause of death was obtained from the National Registry on Mortality. Information on MI was obtained from the hospital diagnosis registry and patient records. This information will contain the complete information on all admissions to the only hospital providing care for acute diseases for the present patient population. For the diagnosis of acute MI, one of the following should be fulfilled; (1) pathological Q waves developing in at least two leads, (2) symptoms suggestive of acute MI or nondiagnostic ECG changes and typical elevated levels of biochemical markers with CK-MB(mass) $\geq 10 \mu\text{g/l}$, (3) symptoms suggestive of acute MI and ST-segment elevation or LBBB and further diagnostics not possible, or (4) signs of acute MI at autopsy.¹²

Statistical Analyses

All data analysis was performed using the Statistical Package for Social Sciences (SPSS 10.1) software (SPSS Inc., Chicago, IL, USA). Kappa statistics were used to assess agreement for categorical data. A kappa value of 1 will represent a perfect agreement, whereas a kappa value of zero will represent an agreement expected by chance alone. For each kappa value, a 95% confidence interval was calculated. For quantitative data, scatter diagrams were constructed and correlation coefficient, mean difference, and standard deviation (SD) calculated. For the analysis of postural ECG changes, only descriptive statistics were used. The Kaplan-Meier method was used to illustrate the timing of events during follow up with statistical assessment using the log-rank test with $P < 0.05$ considered as significant. Relative risk of cardiac event was calculated using univariate Cox regression analysis.

Table 2. Observer Agreement. ST Episode: ST Deviation ≥ 0.1 mV**A. Interobserver**

		Observer 2		
		No ST Episodes	ST Episodes	Total
Observer 1	No ST episodes	67	6	73
	ST episodes	5	22	27
	Total	72	28	100

Kappa (95% confidence interval) = 0.72 (0.57–0.87).

B. Intraobserver

		Observer 1 2 nd Time		
		No ST Episodes	ST Episodes	Total
Observer 1 1 st time	No ST episodes	73	0	73
	ST episodes	3	24	27
	Total	76	24	100

Kappa (95% confidence interval) = 0.92 (0.83–1.00).

RESULTS**Observer Variability**

The inter- and intraobserver agreements, using the two different criteria of an ST episode,

are shown in Tables 2 and 3. When an ST episode was defined according to criterion 1 (transient ST depression or ST elevation of ≥ 0.1 mV), the two observers agreed in 89 patients and disagreed in 11, resulting in a kappa

Table 3. Observer Agreement. ST Episode: ST Depression ≥ 0.05 or ST Elevation ≥ 0.1 mV**A. Interobserver**

		Observer 2		
		No ST Episodes	ST Episodes	Total
Observer 1	No ST episodes	26	32	58
	ST episodes	4	38	42
	Total	30	70	100

Kappa (95% confidence interval) = 0.32 (0.17–0.47).

B. Intraobserver

		Observer 1 2 nd Time		
		No ST Episodes	ST Episodes	Total
Observer 1 1 st time	No ST episodes	55	3	58
	ST episodes	7	35	42
	Total	62	38	100

Kappa (95% confidence interval) = 0.79 (0.67–0.91).

Figure 1. Scatter diagram illustrating the agreement (A) between observer one and observer two and (B) between observer one first time and observer one second time, concerning, maximal ST deviation (top panel) and total duration of ischemia (bottom panel) in patients with ST deviations ≥ 0.1 mV according to both observers (observations).

value of 0.72 (Table 2A). When the first and second interpretation of observer one were compared, there was an agreement in 97 patients and a disagreement in 3 ($\kappa = 0.92$) (Table 2B). A definition of an ST episode as a transient ST depression of ≥ 0.05 mV or an ST elevation of ≥ 0.1 mV (criterion 2) resulted in poorer inter- ($\kappa = 0.32$) and intraobserver ($\kappa = 0.79$) agreement (Table 3).

The concordance between the two observers concerning the maximal ST deviation and total duration of ischemia in the 22 patients with ST episodes according to both observers, is shown in Figure 1A. For the maximal ST-segment deviation, the correlation coefficient was 0.99

($P = 0.01$) and the mean difference was 0.002 mV with a standard deviation of 0.03 mV. For the total duration of ischemia, the agreement was less good with a correlation coefficient of 0.55 ($P = 0.01$), mean difference of 15 minutes, and standard deviation of 93 minutes. The intraobserver comparison concerning maximal ST deviation resulted in a correlation coefficient of 0.98, mean difference of 0.002 mV, and standard deviations of 0.04 mV (Fig. 1B). The corresponding data concerning the total duration resulted in a correlation coefficient of 0.95 ($P = 0.01$), mean difference of 5 minutes, and standard deviation of 22 minutes (Fig. 1B).

Table 4. Maximal ST Segment Change (mV) in Relation to ECG Locations and Body Position

Position	Location	Median	25 th –75 th Percentile	Range
Right lateral recumbent position	Anterior	0.02	0.02–0.04	0.01–0.12
	Inferior	0.02	0.01–0.02	0.01–0.12
	Lateral	0.02	0.01–0.03	0–0.08
Left lateral recumbent position	Anterior	0.04	0.02–0.05	0.01–0.14
	Inferior	0.02	0.01–0.02	0–0.06
	Lateral	0.03	0.02–0.08	0.01–0.17
Recumbent 45° angle	Anterior	0.02	0.02–0.03	0–0.05
	Inferior	0.01	0.01–0.02	0–0.05
	Lateral	0.02	0.01–0.02	0–0.05
Sitting 90° upright	Anterior	0.02	0.02–0.03	0–0.06
	Inferior	0.02	0.01–0.03	0.01–0.05
	Lateral	0.02	0.01–0.02	0–0.05

ST Changes Due to Changes in Body Position

The maximal ST-segment change in relation to ECG location and body position are given in Table 4. The number of patients with ST changes during changes in body position that fulfilled criteria 1 and 2 is shown in Table 5. Both patients with an ST deviation ≥ 0.1 mV in the right lateral position, also had changes in the left lateral position. Out of eight patients with ST deviation ≥ 0.1 mV, three had signs of left ventricular hypertrophy, three T-wave inversions, one ST-segment elevations, and one a normal ECG in supine position. ST deviations ≥ 0.1 mV were present in the lateral leads in six patients, whereas ST deviations ≥ 0.1 mV in the anterior and inferior leads were present in three and one, respectively. Most of the ECG changes with ST deviations ≥ 0.1 mV were accompanied by a sudden change in the QRS-T voltage (Figure 2).

Prediction of Outcome

Out of the 630 patients in set C, 163 (26%) were classified as having an acute MI, 192 (30%) unstable angina or angina, while 64 (10%) were consid-

ered to have other cardiac causes to their symptoms, and 211 (33%) noncardiac or unknown causes. During follow-up there were 24 (3.8%) cardiac deaths and 44 (7.0%) MIs.

The ST monitoring was started immediately on admission. The median time from onset of symptoms to admission was 4.9 (25th–75th percentile: 2.3–10.2) hours. There were 417 (66.2%) patients who had no ST episodes, 113 (17.9%) patients with minor ST episodes fulfilling criterion 2 but not criterion 1, and 100 (15.9%) patients with ST episodes fulfilling criterion 1. Out of those who had ST episodes fulfilling criterion 1, 87 patients had only episodes of ST-segment depressions, five patients had only ST-segment elevation, and eight patients had both depressions and elevations of the ST segment. During follow-up there were 7 (1.7%), 4 (3.5%), and 13 (13%) cardiac deaths in the group with no ST episodes, minor ST episodes, and ST episodes fulfilling criterion 1, respectively (Fig. 3A). The corresponding event rates concerning cardiac death or MI were 18 (4.3%), 6 (5.3%), and 24 (24%) (Fig. 3B). When patients were categorized according to ECG on admission or to diagnosis, ST

Table 5. Number of Patients Fulfilling the Two Tested Criteria in Different Body Positions

	ST Depression ≥ 0.1 mV or ST Elevation ≥ 0.1 mV	ST Depression ≥ 0.05 mV or ST Elevation ≥ 0.1 mV
Right lateral recumbent position	2 (4%)	7 (14%)
Left lateral recumbent position	8 (16%)	21 (42%)
Recumbent 45° angle	0	1 (2%)
Sitting 90° upright	0	2 (4%)

Figure 2. Four examples of ECG changes due to changes in body position. Supine position: ----; Lateral position: —. The ST levels are changed due to changes in the QRS and T-wave voltage. The T waves pull the ST levels upward or downward.

episodes fulfilling criterion 1 predicted a poor outcome in all subgroups (Table 6).

DISCUSSION

In patients with unstable CAD, transient ST changes during Holter recording have been related to a higher rate of multivessel disease and subsequent cardiac events.⁵⁻⁷ However, a disadvantage with Holter recording is the off-line analysis, which means that information obtained may reflect events occurring several hours or days earlier. Another problem with Holter recording is the use of only two or three leads. In a previous study, 12-lead monitoring was shown to be a more sensitive method to detect ischemia compared to 3-lead monitoring.³ Therefore, the use of on-line monitoring with continuous 12-lead ECG in intensive care

units, coronary care units, chest pain units, and catheter laboratories has recently increased.

Observer Variability

A major concern with any diagnostic method that requires interpretation is the user-dependency of the method. In the present study, the agreement between one experienced observer and one newly trained observer was good regarding presence or absence of conventionally defined ST episodes (≥ 0.1 mV for ≥ 1 minute). The agreement was also good concerning the maximal ST deviation during an ST episode. Thus, based on a short period of training this method seems reliable as an indicator of transient ischemic episodes and for measuring the maximal ST-segment deviation compared to baseline ECG.

Figure 3. Cumulative probability and time of occurrence of (A) cardiac death, (B) cardiac death or myocardial infarction in patients with no ST episodes, patients with minor ST episodes fulfilling criterion 2 (ST depression ≥ 0.05 mV or ST elevation ≥ 0.1 mV) but not criterion 1 (ST depression or elevation ≥ 0.1 mV), and patients with ST episodes fulfilling criterion 1.

However, concerning the total duration of ischemia the interobserver variability was large. Although the large variation was partly caused by large differences in a few patients, this still indicates a problem with the method. One reason for the discrepancy was probably differences in the evaluation of possible artefacts and nonischemic ST changes, e.g., due to changes in body position and heart rate. Another reason might be presence of ST deviation at the start of monitoring. This will affect the selection of reference ECG, which will influence the duration of ischemia substantially.

This raises questions about the usefulness of measuring duration of ischemia and "total ischemic burden" as a product of time and degree of ST

deviation with the current method.¹³ However, this first study on observer variability during continuous 12-lead ECG involved only one pair of observers. Additional studies on the reproducibility of the method are needed, before a final evaluation can be done.

ST Changes Due to Changes in Body Position

The most common cause of nonischemic ST changes is changes in body position.¹⁴ When using ST monitoring as an indicator of reperfusion during thrombolysis, the patient is usually sedentary in reclining or supine position and postural ST change

Table 6. Relative Risk of Cardiac Death or Myocardial Infarction in Patients with ST Episodes

Subgroup	n (%)	Relative Risk (95% CI)
ECG on admission		
No ST-T changes (n = 258)	10 (3.9)	5.68 (0.63–50.0)
ST segment depression (n = 189)	64 (34)	2.63 (1.15–5.99)
LVH or isolated T-wave inversions (n = 183)	26 (14)	6.58 (2.72–15.9)
Diagnosis within 24 hours		
Acute myocardial infarction (n = 163)	67 (41)	2.09 (1.06–4.12)
No acute myocardial infarction (n = 467)	33 (7.1)	3.92 (1.07–14.3)

N: Number of patients. CI: Confidence interval. LVH: Left ventricular hypertrophy.

usually is a minor problem. However, during ST monitoring in patients with unstable coronary artery disease postural ST changes may cause problems in the analysis.

In the present study, patients investigated regarding postural ST changes had a high incidence of T-wave inversions and signs of left ventricular hypertrophy, known to be associated with a high incidence of postural ST changes.^{15,16} Still, these ST changes were usually small but reached significant levels in 8 (16%) patients, most commonly in the lateral leads in the left lateral position. These findings are consistent with previous studies investigating positional changes during ST monitoring.^{15,16} The positional ST changes can usually be recognized by simultaneous changes in the overall QRS-T voltage, which seems to pull the ST level upward or downward (Fig. 2). However, ischemic QRS changes also may be associated with changes in QRS amplitude.¹⁷ Thus, concerning some ST changes problems may arise in the differentiation between ischemia and changes in body position. Different solutions have been suggested to this problem, such as the use of body position sensors,¹⁸ the use of mathematical algorithms, and creation of "ECG-templates" from different body positions which then can be used for comparison.¹⁵

Optimal Criterion of ST-Segment Change

It is now well established that occurrence of transient ST depression or ST elevation ≥ 0.1 mV during ST monitoring may represent myocardial ischemia.¹⁹⁻²¹ However, the criteria resulting in the highest accuracy to detect myocardial ischemia in patients with unstable CAD, are difficult to define. It could be hypothesized that the optimal criteria might be identified during percutaneous coronary interventions. However, occlusion of a coronary artery at balloon dilatation most often leads to ST elevation.²² Thus, this situation does not adequately reflect the fluctuating flow limitation in the culprit coronary artery and the subendocardial ischemia in unstable CAD.

Recently, ST-segment depressions < 0.1 mV in the standard 12-lead ECG were shown to predict a worse outcome after an episode of unstable CAD.^{7,8} Also, in a previous study, using continuous 12-lead ECG monitoring, transient ST changes < 0.1 mV were suggested to have clinical significance.³ The usefulness of ST depression episodes < 0.1 mV was, however, not supported by the

present study. When transient ischemic episodes were defined as ST depression ≥ 0.05 mV or ST elevation ≥ 0.1 mV, the inter- and intraobserver agreement was poor, and more than 40% of the patients were considered to have ischemic episodes when changing body position. Furthermore, the occurrence of ST depression episodes 0.05-0.1 mV did not carry any prognostic information concerning subsequent cardiac events. In contrast, the conventional criterion of ST episodes (≥ 0.1 mV), resulted in acceptable inter- and intraobserver agreement, less problems with positional artefacts, and clinically important prognostic information concerning the risk of future cardiac events.

CONCLUSION

At continuous 12-lead ECG monitoring of chest pain patients, ST deviations of less than 0.1 mV seem to have a low specificity and limited clinical significance. ST episodes, defined as ST deviations ≥ 0.1 mV, on the other hand, have a low inter- and intraobserver variability, minor problems with postural artefacts, and an important diagnostic and prognostic value.

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