European Heart Journal (1997) **18**, 931–940

Comparison of usefulness of computer assisted continuous 48-h 3-lead with 12-lead ECG ischaemia monitoring for detection and quantitation of ischaemia in patients with unstable angina

P. Klootwijk*, S. Meij*, G. A. v. Es†, E. J. Müller‡, V. A. W. M. Umans§, T. Lenderink† and M. L. Simoons*

**Division of Cardiology, Thoraxcenter, University Hospital Dijkzigt, Erasmus University Rotterdam, The Netherlands; †Data processing center Cardialysis B.V., Rotterdam, The Netherlands; ‡Division of Cardiology, Spaarne Ziekenhuis, Heemstede, The Netherlands; §Division of Cardiology, Medisch Centrum Alkmaar, Alkmaar, The Netherlands*

Aims The selection of ECG leads used for ST monitoring may influence detection and quantitation of ischaemia.

Methods We compared on-line continuous 48-h 12-lead against 3-lead ST monitoring in 130 unstable angina patients (Mortara, ELI-100). Onset and offset of ST episodes were defined by the lead with the first ≥ 100 μV ST change relative to baseline and the lead with the latest return to baseline ST level, respectively. ST episodes were calculated for 12 leads and 3 leads (V_2, V_5, III) separately.

Results ST episodes were detected in 88 patients (77%) by 12-lead and in 71 patients (62%) by 3-lead ST monitoring ($P<0.02$). The median number (25, 75%) of episodes/patient was 1 (0, 3) for 3-lead and 2 (1, 6) for 12-lead ($P<0.0001$). The total duration of ischaemia detected during 12-lead far exceeded 3-lead monitoring: 12·3 (1, 58·2) and 1·7 (0, 23·3) min respectively ($P<0.0001$). The probability of recurrent ischaemia declined most during the first 24 h of monitoring. After a period without ST changes of 1, 12, 24 and 36 h, the probabilities of recurrent ischaemia were 63, 31, 14 and 9%, respectively.

Conclusions Continuous 12-lead ST monitoring increases detection rate and duration of ST episodes compared to 3-lead ST monitoring. The use of continuous 12-lead ECG monitoring devices on emergency wards and coronary care units is recommended.
(Eur Heart J 1997; 18: 931–940)

Key Words: ST monitoring, unstable angina, ECG leads.

Introduction

Patients with unstable angina may suffer from early unfavourable cardiac events in spite of intensive medical therapy. Prognosis is defined primarily by the recurrence and severity of silent or symptomatic myocardial ischaemia and by the presence of multivessel coronary artery disease[1–7]. The assessment of the total ischaemic burden and the identification of patients at risk should preferably be based on continuous ECG monitoring techniques. Continuous ST monitoring, whether on-line or by Holter recording with subsequent off-line analysis, has been limited by a restricted number of 2 or 3 ECG leads. Recently, new systems have been introduced for continuous on-line analysis of 12-leads or orthogonal vector lead ECGs, which have overcome the limitations of these earlier technologies[8–12]. However, the additional value of 12-lead ECG analysis over 2 or 3 leads or single lead analysis in patients with unstable angina is not reported. Comparative studies of different lead systems have been performed to address the value of multilead exercise electrocardiography[13–15]. These results, however, may not be applicable to patients with unstable angina, since the pathophysiology of unstable angina differs from the pathophysiology of stable angina (plaque rupture and coronary thrombosis vs fixed stenosis with ischaemia due to increased myocardial oxygen consumption).

The aim of the present study was to compare continuous 12-lead ST monitoring with more conventional 3-lead ST monitoring for detection and

Revision submitted 2 August 1996, and accepted 9 August 1996.

Correspondence: A. P. J. Klootwijk MD, Thoraxcenter Ba 316, Erasmus University Rotterdam, University Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

0195-668X/97/060931+10 $18.00/0

quantitation of ischaemia in patients with unstable angina, and to investigate which leads most frequently contribute to the detection of ST episodes. A new algorithm for detection and quantitation of ischaemic events is presented, which takes into account all 12 ECG leads simultaneously.

Methods

Study patients

One hundred and thirty patients, who were hospitalized for unstable angina and who participated in a dose-finding study of a new anti-thrombin agent, underwent continuous 12-lead ST monitoring in 18 hospitals (see appendix)[16,17]. Patients were eligible for the study if an episode of chest pain was accompanied by dynamic ST and/or T wave changes indicative of myocardial ischaemia. Patients with ECG abnormalities, such as left bundle branch block, left ventricular hypertrophy or artificial pacemaker device, making ST segment interpretation unreliable, were excluded, as were patients with a recent myocardial infarction.

Continuous ST monitoring

Continuous ECG monitoring was performed using the ELI-100 continuously updated 12-lead ECG monitoring system (Mortara Instruments, Milwaukee, U.S.A.), which automatically calculates median ECG complexes of the 12 ECG leads every 15 s. The system was programmed to store median ECG complexes every 20 s if $\geq 100\,\mu V$ ST segment shift was present in one lead relative to the baseline ECG of that patient, or if $\geq 50\,\mu V$ ST shift was present in any two leads of the 12-lead ECG. If little or no ST change was present, a baseline median ECG was stored every 20 min.

Median ECG complexes and ST trend data were stored on a removable hard disk or floppy disk. After completion of the recording, this disk was sent to the Cardialysis core laboratory (Rotterdam, The Netherlands) for subsequent editing and analysis.

Editing and analysis of recorded data

Before editing, the 12-lead ECG templates at the start of the continuous ECG recording were compared with the study entry 12-lead ECGs in order to verify proper lead placement. In the case of discordance, the recording was rejected.

All median QRST templates were manually scanned and edited for artifacts, intermittent bundle branch block, detection or marker errors and postural changes. The latter was defined as a sudden change of the frontal QRS axis and/or a sudden QRS amplitude change from V_1 to V_6 or vice versa. After editing, the trends of the ST segment level measured at the J-point+60 ms were generated for each single lead of the 12-lead ECG, except aVR.

Reference ECG

At study entry, an attempt was made to document both a standard 12-lead ECG during chest pain and a 12-lead ECG without chest pain. These ECGs were used to define a reference 'non-ischaemic' (without chest pain) median ECG complex during the continuous ECG recording. If the median ECG complex at the start of the recording was similar to the study entry non-ischaemic 12-lead ECG, this ECG complex was used as the reference 'non-ischaemic' continuous ECG complex. If the first ECG complex was not similar to the study-entry non-ischaemic 12-lead ECG, attempts were made to identify the most comparable 'non-ischaemic' ECG complex of the continuous ECG recording. Subsequently, this ECG complex was used as the reference 'non-ischaemic' ECG.

Definition of ST episodes

The onset of an ST episode was defined as a change of ST-amplitude in one or more leads of at least $\pm 100\,\mu V$ from the baseline ST level, developing within a 10 min period and persisting for at least 1 min. The end of an episode was defined as a return of the ST level within $\pm 100\,\mu V$ of the baseline ST level, again lasting for at least 1 min. Episodes had to be separated from each other by at least 1 min. If $\geq 100\,\mu V$ ST change was present in more than one lead simultaneously, the episode onset was defined by the lead exhibiting the first significant ST change. Similarly, the end of an episode was defined by the lead exhibiting the latest return to baseline ST level. An example of the ST trend analysis and representative ECG recordings is presented in Figs 1 and 2.

Automated detection of ST segment changes $\geq 100\,\mu V$

An algorithm programmed according to the previously described ST criteria for ischaemia was applied to each single lead ST trend, in order to detect both the time and ST values of onset and offset of an ST episode and its peak ST level. In order to prevent a reversal of baseline with a real ST episode (or false detection of an untrue ST episode), the algorithm was programmed to skip episodes of which the onset ST value was closer to the initial reference ST level than the baseline ST level during the predefined 10 min window. In such an instance, the ST value was used as baseline update for the detection of a possible next episode.

Subsequently, the digital trend analysis was confirmed by a second visual analysis of the real-time ECG, thus double checking template quality and excluding

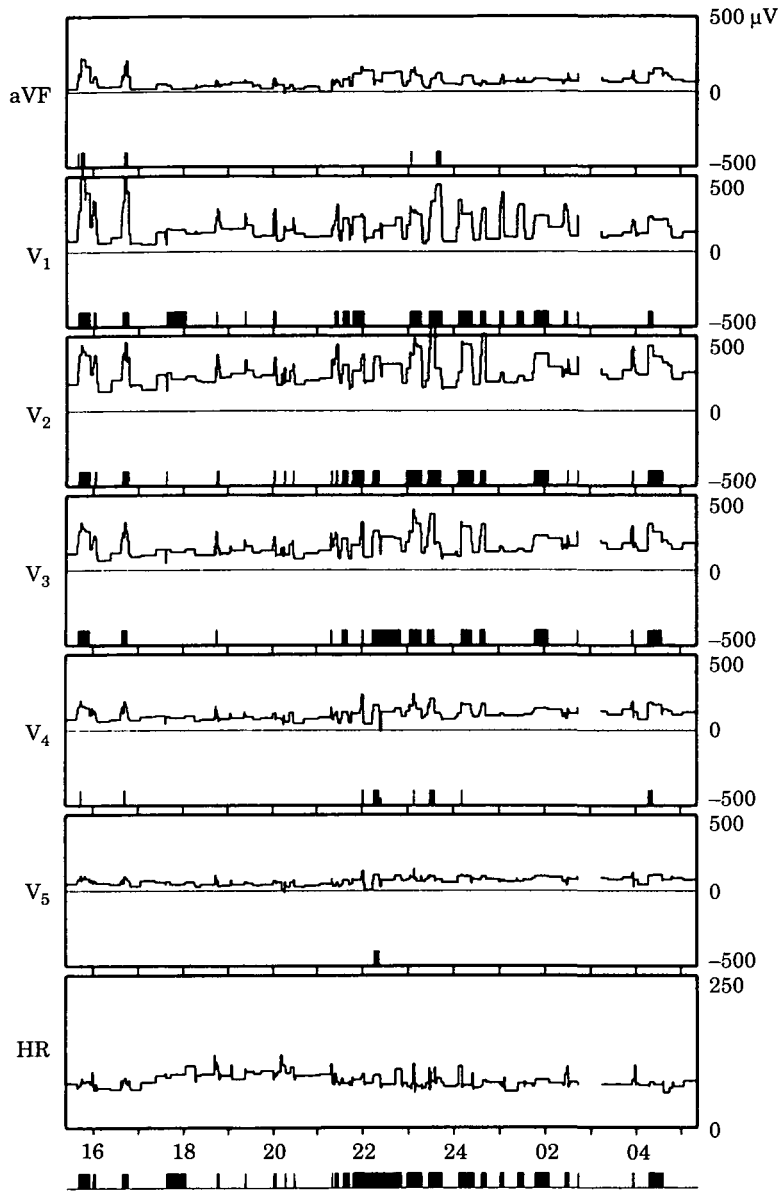

Figure 1 **Twelve-lead ST analysis in a patient with unstable angina. The ST trends of those leads in which ST episodes occurred are displayed, together with the heart rate trend (bottom trend curve). The black bars in each single lead ST trend represent the time during which the algorithm detected a ≥ 100 μV ST change. At the bottom of the trend graphs, the black bars indicate the total ST episode duration (ischaemia) taking into account all leads involved.**

false-positive or false-negative automated ST measurements. The ECG at moments of interest, either detected by the algorithm or by the operator, was documented on hard copy for visual inspection (Fig. 2).

ST episodes based on 12-lead and 3-lead ST trends

As a final summary analysis, the total number of ST episodes was calculated based on both the combination of either 3 leads III, V_2 and V_5 or the combination of all 12 leads (except aVR).

Statistical analysis

Continuous variables are expressed as median and interquartile range (25th and 75th percentiles). Unpaired variables were compared using the Mann–Whitney test. Wilcoxon signed rank test was used for paired variables. Discrete variables are described with percentages and

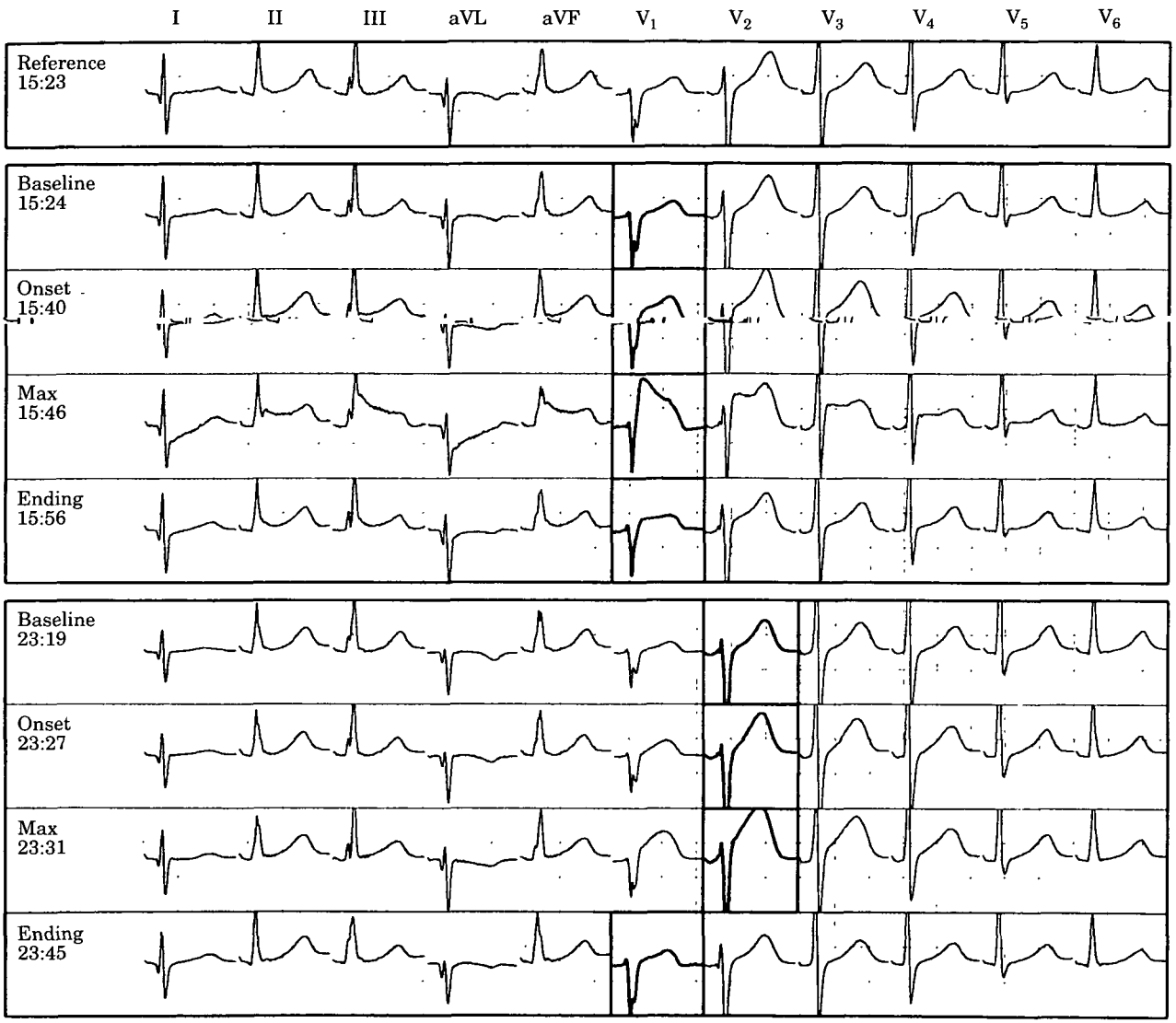

Figure 2 **Samples of the computer-assisted 12-lead ECG recording of the patient in Fig. 1. The upper ECG row demonstrates the 12-lead ECG (except aVR) which has been selected as the reference, 'non-ischaemic' ECG. The ECG rows directly below demonstrate the time and ECG lead (indicated in bold) in which the ST episode occurred. In the upper panel, ST changes are present in multiple leads, but the ST changes of V_1 appear dominant. Thus the onset, maximum and ending of the episode is detected in this lead. However, in another episode shown in the lower panel, the onset and maximum of the ST episode is detected in lead V_2, but the end of this combined episode is detected in lead V_1.**

were compared using the chi-square test. The number of episodes per patient during 3-lead and 12-lead ST monitoring might differ in two directions, since both more and less frequent ST episodes might be detected by 12 leads compared with 3 leads. The latter might be due to combining of multiple short episodes in one long episode. This would result in fewer episodes but a longer ischaemic duration. Therefore, a two-tailed *P* value was calculated in all instances. A *P* value of $\leq 0{\cdot}05$ was considered statistically significant. The Kaplan–Meier method was used for the evaluation of the time to the occurrence of a first ST episode and the possibility of a recurrent ST episode, with censoring of data. Statistical difference was tested with the Log rank test.

Results

ECG monitoring was initiated in 130 patients. Good quality recordings were eventually obtained in 114 patients (88%). The median (25, 75 percentiles) total ECG monitoring time was 53 (49, 55) h. Total analysable ECG monitoring time was 44 (38, 48) h. Twelve-lead ST monitoring detected 515 ST episodes suggestive of transient ischaemia against 311 for 3-lead ST monitoring, respectively (Table 1, $P<0{\cdot}0001$). This resulted in detection of ischaemia by 12-lead ST monitoring in 88 patients (77%) vs 71 patients (62%) by 3-lead ST monitoring ($P=0{\cdot}02$). Sixty-four of the 88 patients with ST episodes during 12-lead monitoring had more than one

Table 1 Summary of ST analysis parameters. Comparison of computer-assisted 3-lead against 12-lead ST monitoring in 114 patients with unstable angina

n=114	3-lead ST monitoring	12-lead ST monitoring	*P* value
ST episodes present (pts)	71 (62%)	88 (77%)	0·02
>1 ST episode present (pts)	46	64	0·02
Total number of episodes	311	515	<0·0001
Patients with symptomatic ST episodes	10 (9%)	10 (9%)	ns
Number of episodes/pt*	1 (0, 3)	2 (1, 6)	<0·0001
Total duration (min) of ST shift/pt*	1·7 (0, 23·3)	12·3 (1, 58·2)	<0·0001
Duration of ST episode (min)**	5 (1·3, 17·7)	7 (1·3, 20)	<0·0001
Mean duration of episode/pt (min)**	7·7 (1·8, 14·4)	10·2 (2·6, 15·2)	0·03
Time to first episode (hrs)**	12·7 (5·8, 28·4)	9·9 (4·0, 21·2)	<0·0001

*median, 25, 75 percentiles, including patients without ischaemia.
**median, 25, 75 percentiles, patients with ischaemia only.

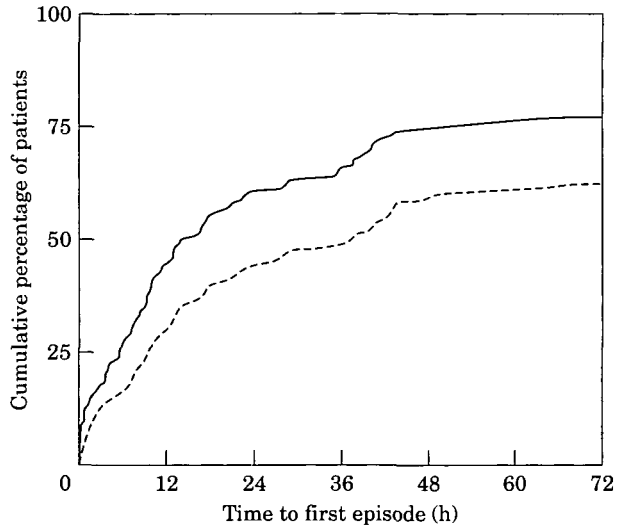

Figure 3 **Time to the occurrence of the first ST episode after the start of ST monitoring plotted against the cumulative percentage of patients. ———=12-lead; – – –=3-lead.**

ST episode (73%), against 46 (65%) of the 71 patients during 3-lead monitoring (P=0·02).

Several other observations support the greater sensitivity for detection of ST segment changes of 12-lead monitoring over 3 leads. For example, the first ST episode during monitoring was detected earlier by 12 leads (Table 1 and Fig. 3), and the duration of ischaemia detected by 12 leads exceeded the duration in 3 leads (Fig. 4). Furthermore, the number of leads involved per ST episode was higher for 12-lead than for 3-lead ST monitoring (Table 2).

For 12-lead ST monitoring, episodes with precordial lead involvement only were far more frequently present than episodes with only standard or augmented lead involvement (77% against 11% respectively, P<0·0001). Simultaneous involvement of both the standard or augmented leads and the precordial leads was present in 60 out of 515 ST episodes (12%). A shift of ST episodes from either the standard or augmented leads to the precordial leads or vice versa occurred in 20 (31%) of the 64 patients who had more than one ST episode during 12-lead ST monitoring. For 3-lead ST monitoring, the single lead episodes of V_2 contributed most to the detection of the onset of ST episodes (Fig. 5, panel B, P<0·0001), while V_2, V_3 and V_4 were equally sensitive in the 12-lead analysis (Fig. 5, panel A).

Figure 6 shows a Kaplan–Meier 'survival' analysis with censoring of data of the probability to remain free of a new ST episode during the course of the monitoring period using 12 leads. The probability of a recurrent ST episode declined most during the first 24 h of monitoring. There was no difference between the probability of occurrence of a new ST episode after the start of the ECG monitoring period or the probability of recurrence of a second ST episode after the first, or a third after the second episode.

Forty-five patients (39%) had at least one episode of chest pain during ECG monitoring. However, ST changes of $\geq 100\ \mu V$ were present during those episodes in 10 patients only (22%), during both 3- and 12-lead ECGs. If additional less prominent ST and T wave changes similar to the study entry ECG were also taken into account, ECG signs of ischaemia were present during chest pain in 26 patients (58%). There was no significant difference between the number of ST episodes in patients with and without episodes of chest pain.

Nineteen patients (17%) suffered from an in-hospital cardiac event and/or underwent emergency angiography within the first 7 days of admittance to hospital. There were no cardiac deaths. Clinical events occurred more frequently in patients with chest pain during the monitoring period and in patients with chest pain and concomitant ST episodes compared to those without recurrent ischaemia (Table 3). These observations were, however, not statistically significant in this small series of patients.

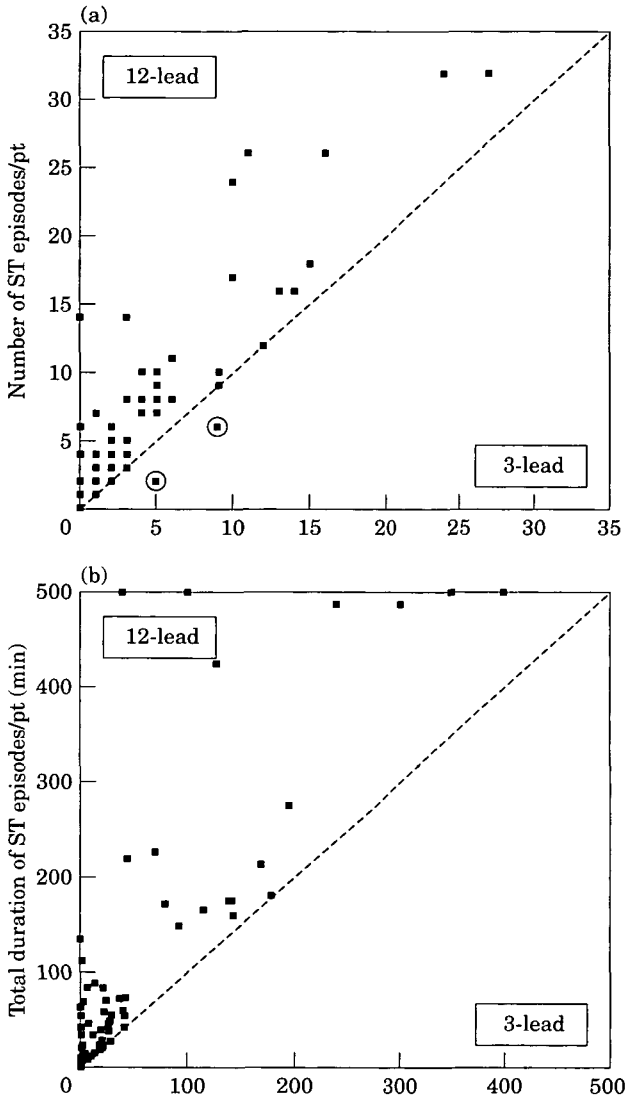

Figure 4 **Comparison of 12-lead and 3-lead ST monitoring. Panel (a) demonstrates the number of episodes per patient for both techniques, panel (b) the duration of the ST episodes per patient. Note: Single dots may represent more than one patient. The encircled patients in panel (a) show more episodes during 3-lead than 12-lead ST monitoring. In these patients, several isolated 3-lead ST episodes appeared to be part of one, longer lasting 12-lead ST episode, depending on the leads involved.**

Discussion

Recently, computer assisted continuous 12-lead ECG monitoring techniques have become available for real-time ECG and ST segment monitoring in patients with acute coronary syndromes[8,9,18]. These techniques have outgrown the limitations of serial ECG recording, which provides snapshot information only, and Holter ST recording, which is limited by a restricted number of leads and allows for retrospective off-line analysis only.

In patients with an acute myocardial infarction receiving thrombolytic therapy, computer assisted continuous ECG monitoring has proven to be of clinical value for prediction of vessel status and identification of high risk patients[10–12]. However, so far, no systematic studies have been conducted to evaluate the usefulness of computer-assisted continuous 12-lead ECG monitoring techniques in patients with unstable angina. To our knowledge, this study is the first to demonstrate the relationship between detection and quantitation of ischaemia and ECG monitoring technology in these patients. Twelve lead ST monitoring appeared to be more sensitive than the more generally applied 3-lead technology. When only three leads were used for ST monitoring, ischaemia was detected in 62% of patients, which is comparable to studies using Holter ST monitoring in patients with unstable angina[1,19]. With 12-lead ST monitoring, ischaemia was detected in an additional 15% of patients. Both the number and duration of ischaemic episodes far increased using 12-lead compared to 3-lead ST monitoring.

The ST changes were found to disperse and shift among different leads in time in at least 31% of patients with more than one ST episode during the monitoring period. This may depend on the flow balance of the coronary system, the degree of vessel injury and the duration and severity of ischaemia. Thus, instead of monitoring the lead with maximal ST deviation or sum ST deviation in patients with myocardial infarction[20,21], full 12-lead ST monitoring should be preferred for detection and quantitation of ischaemia in patients with unstable angina. The major differences between ST monitoring of unstable angina patients vs ST monitoring of acute myocardial infarction patients are listed in Table 4.

Table 2 ***Number of leads involved per ST episode. Comparison of computer-assisted 3-lead and 12-lead ST monitoring***

Lead selection	Number of leads involved per ST episode (%)						Total number of ST episodes
	1	2	3	4	5	>5	
3 leads	252 (81)	47 (15)	12 (4)	—	—	—	311
12 leads	283 (55)	97 (19)	63 (12)	24 (5)	14 (3)	34 (7)	515

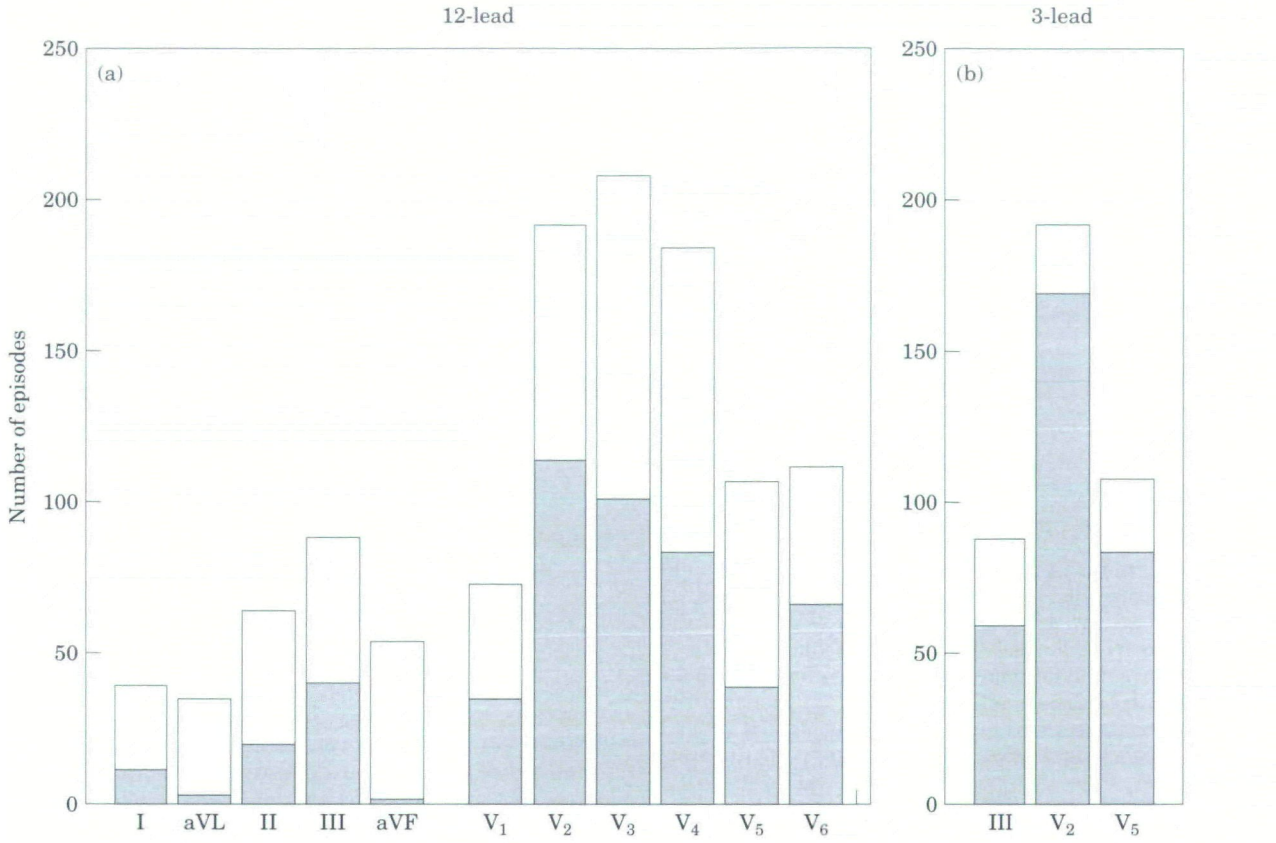

Figure 5 **Number of single ST episodes per lead and detection of earliest ST episode onset if all leads involved are taken into account. The bars represent the number of ST episodes detected in each single lead. The tinted areas represent the number of episodes which detected the earliest episode onset. Panel (a) detection of onset of ST episodes when using 12-lead ST monitoring; Panel (b) detection of onset of ST episodes when using leads III, V_2 and V_5 only.**

ST episodes were most frequently present in the leads V_2, V_3 and V_4. In addition, these leads also contributed most to the detection of the onset of ST episodes if all involved leads were taken into account. This is in contrast to previous studies on body surface mapping and optimal lead placement during exercise electrocardiography in patients with coronary artery disease[13–15]. These studies demonstrated that the single lead with the greatest sensitivity for detecting ST segment shift was between the right infraclavicular region area and the V_5 position, which is in fact a bipolar V_5 lead. Our data do not support these findings and suggest that studies on lead placement and ST shift during exercise testing in patients with stable angina may not be applicable to patients with unstable angina in whom both the underlying pathophysiological mechanism and the extent and area of ischaemia is different[22]. In addition, our results indicate that ST episodes with only standard lead involvement are rare. As such, it is conceivable that the applied cut-off value of $\geq 100\,\mu V$ ST change is not adequate for standard lead monitoring in general practice.

Previous studies on patients with unstable angina demonstrated that recurrent ischaemia occurs most frequently in the first 24–48 h of admission to hospital[22,23]. This is in concordance with our finding that the majority of patients exhibited a recurrence of ischaemia within the first 15 h of ST monitoring, with only 23% of patients remaining free of an ST episode during the total monitoring period (Fig. 3). In addition, Fig. 6 demonstrates that the distribution of the occurrence of an ST episode over time was similar for the first interval since the start of the ST monitoring period, as well as for the occurrence of a second episode after the first and a third after the second. This suggests similar underlying pathophysiological mechanisms of these episodes[23]. Apparently, plaques stabilize and become quiescent' after a period without recurrent ischaemia of approximately 24 h.

In agreement with Holter ST studies in patients with unstable angina, ST changes of $\geq 100\,\mu V$ during moments of chest pain were infrequently present, occurring in only 22% of the patients with chest pain during the monitoring period[19,24,25]. This may be due to at least three factors: (1) complaints may not always be of ischaemic origin, (2) the time of occurrence of complaints may not always have been correctly indicated by the patient or annotated in the case record forms, (3) the

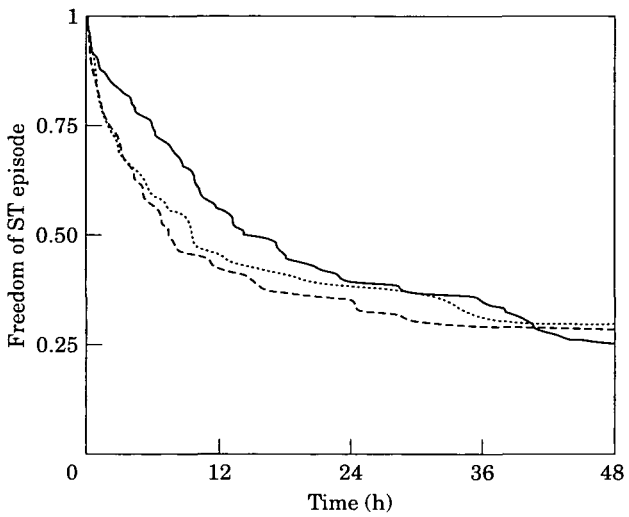

Figure 6 **Kaplan–Meier event free survival estimate. The curves indicate the probability of remaining free of an ST episode during the course of the monitoring period: (1) from start of the monitoring period (——, median time 15·3 h), (2) from the end of the first ST episode until the second (– – –, median time 7·4 h) and (3) from the end of the second ST episode until the third (. . . . , median time 9·6 h), using 12-lead ST monitoring. The curves virtually overlap, suggesting similar pathophysiology for the different episodes. Plaques apparently become quiescent after a period without ischaemia of approximately 24 h.**

generally accepted $\geq 100\,\mu V$ ST change criterion for detection of ischaemia may be too insensitive to pick up minor ischaemic ECG changes that may occur in these unstable patients. The latter assumption is supported by the fact that minor ST and T wave changes, similar to the study entry ECG during pain were present during pain in 58% of all patients who had episodes of chest pain during the recording. This implies that not only ST changes of $\geq 100\,\mu V$ but also smaller ST and T wave changes should be taken into account as signs of ischaemia in these patients. Until recently, the standardization and automated detection and quantitation of these minor ST and T wave changes was hampered by the limitations of earlier ECG technologies such as Holter, because of baseline drift and restriction of number of leads. In contrast, the high quality ECG signals provided by computer-assisted ECG monitoring technologies have overcome these limitations and may challenge us to develop new ischaemia standards and algorithms for automated detection and quantitation.

Finally, in contrast to other studies using Holter ST recording techniques[1,19], we did not demonstrate a significant difference in the occurrence of in-hospital cardiac events within the first week from admittance between patients with and without ST episodes, although trends were similar to previous studies (Table 3). This may be due to the small number of patients who suffered from an in-hospital clinical event.

Table 3 Correlation of in-hospital cardiac events within 7 days from admission to hospital with the presence of chest pain andlor ST episodes during the ECG monitoring period

During recording	Number of pts	Myocardial infarction	PTCA/CABG	Any clinical event (%)	No clinical event (%)
Chest pain	45	5	7	11 (24)	34 (76)
No chest pain	69	7	1	8 (12)	61 (88)
Chest pain+ST episode(s)	37	4	7	9 (24)	28 (76)
Chest pain+ corr. ST episode	10	0	3	3 (30)	7 (70)
No chest pain,No ST episodes	18	2	0	2 (11)	16 (88)
12 lead, ST episodes present	88	9	8	16 (18)	72 (82)
12 lead, No ST episodes	26	3	0	3 (12)	23 (88)
3 lead, ST episodes present	71	7	7	13 (18)	58 (82)
3 lead, No ST episodes	43	5	1	6 (14)	37 (80)

Table 4 Differences of ST analysis in patients with acute myocardial infarction and unstable angina

Acute myocardial infarction	Unstable angina
ST monitoring of single lead with greatest ST shift will suffice in most instances	Multilead ST monitoring necessary, as the ischaemic area may vary in time. Scanning of different leads for earliest onset, highest peak and latest end of ST episodes is necessary
Baseline ST level is defined by the moment of ST recovery and ST steady state	Baseline ST level is not defined, a reference ECG is necessary
Recurrent ischaemia is reflected by ST re-elevation instead of ST depression in most instances	Ischaemia may be reflected by both ST elevation, ST depression and T wave changes, which makes automated analysis using computer algorithms difficult
Gradual T wave changes only	Minor ST segment and T wave changes may reflect ischaemia, which makes accurate quantitation of ischaemia difficult

We conclude that computer-assisted 12-lead ECG monitoring can be used for on-line ECG ischaemia monitoring of unstable angina patients both for clinical purposes and for quantitation of myocardial ischaemia in studies. The use of continuous 12-lead ST monitoring significantly increased the detection rate of ST episodes as compared to more conventional continuous 3-lead ST monitoring. Furthermore 12-lead ST monitoring yields more episodes and longer duration of ischaemia. Whether this also relates to a better specificity for prediction of impending clinical events could not be established from the small subset of patients who actually suffered an in-hospital clinical event during this study. Computer-assisted 12-lead ECG monitoring systems are recommended on emergency wards and coronary care units, not only for monitoring of patients with an acute myocardial infarction receiving thrombolytic therapy, but also for monitoring of unstable angina patients.

References

[1] Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker of early unfavourable outcomes in patients with unstable angina. N Engl J Med 1986; 314: 1214–9.

[2] Gottlieb SO, Gerstenblith G Assessing the total ischemic burden in the management of unstable angina. Am J Med 1986; 81 (4A): 7–11.

[3] Romeo F, Rosano GM, Martuscelli E, Valente A, Reale A. Unstable angina: role of silent ischemia and total ischemic time (silent plus painful ischemia), a 6-year follow-up. J Am Coll Cardiol 1992; 19: 1173–9.

[4] Nademanee K, Intarachot V, Josephson MA *et al.* Prognostic significance of silent myocardial ischemia in patients with unstable angina. J Am Coll Cardiol 1987; 10: 1–9.

[5] Sharma GVRK, Deupree RH, Luchi RJ, Scott SM and the participants of the Veterans Administration Cooperative Study No. 28. Identification of unstable angina patients who have favourable outcome with medical or surgical therapy (eight-year follow-up of the Veterans Administration Cooperative Study). Am J Cardiol 1994; 74: 454–8.

[6] Sclarowski S, Davidson E, Lewis RF, Strasberg B, Arditti A, Agmon J. Unstable angina evolving to acute myocardial infarction: Significance of ST changes during chest pain. Am Heart J 1986; 112: 459–62

[7] Foley JB, Foley D, Molloy M, Crean PA, Gearty GF, Walsh ML. Acute impact of percutaneous transluminal coronary angioplasty on the ischemic burden in stable and unstable angina. Am Heart J 1993; 126: 705–7.

[8] Dellborg M, Gustaffson G, Riha M, Swedberg K. Dynamic changes of the QRS complex in unstable angina pectoris. Int J Cardiol 1992; 36: 151–62.

[9] Lundin P, Eriksson SV, Erhardt L, Strandberg LE, Rehnqvist N. Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology 1992; 81: 145–56.

[10] Krucoff MW, Croll MA, Pope JE *et al.* Continuously 12-lead ST-segment recovery analysis in the TAMI 7 study. Circulation 1993; 88: 437–46.

[11] Dellborg M, Steg PG, Simoons M *et al.* Vectorcardiographic monitoring to assess early vessel patency after reperfusion therapy for acute myocardial infarction. Eur Heart J 1995; 16: 21–9.

[12] Klootwijk P, Langer A, Meij S *et al.*, for the GUSTO-I ECG-ischemia monitoring substudy. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST-segment monitoring in the GUSTO-I trial. Eur Heart J 1996; 17: 689–98.

[13] Simoons ML, Block P. Toward the optimal lead system and optimal criteria for exercise electrocardiography. Am J Cardiol 1981; 47: 1366–74.

[14] Phibbs BP, Buckels LJ. Comparative yield of ECG leads in multistage stress testing. Am Heart J 1975; 90: 275–6.

[15] Chaitman BR, Bourassa MG, Wagniart P, Corbara F, Ferguson RJ. Improved efficiency of treadmill exercise testing using a multiple lead ECG system and basic hemodynamic exercise response. Circulation 1978; 57: 71–9.

[16] Simoons ML, van Miltenburg A, Scheffer MG *et al.* Anticoagulant properties of efegatran, a direct thrombin inhibitor in patients with unstable angina. Eur Heart J 1994; 15 (Abstr Suppl): 757.

[17] Simoons M, Lenderink T, Scheffer M *et al* Efegatran, a new direct thrombin inhibitor: safety and dose response in patients with unstable angina. Circulation 1994, 90; 4 (Abstr Suppl) 2: 1241.

[18] Gerstenblith G. Treatment of unstable angina pectoris. Am J Cardiol 1992; 70: 32G–37G.

[19] Langer A, Freeman MR, Armstrong PW. ST-segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. J Am Coll Cardiol 1989; 13: 1495–1502.

[20] Clemmensen P, Ohman M, Sevilla DC *et al.* Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. Am J Cardiol 1990; 66: 1407–11.

[21] Klootwijk P, Cobbaert C, Fioretti P, Kint PP, Simoons ML. Noninvasive assessment of reperfusion and reocclusion after thrombolysis in acute myocardial infarction. Am J Cardiol 1993; 72: 75G–84G.

[22] Braunwald E. Unstable angina. A classification. Circulation 1989; 80: 410–4.

[23] Miltenburg-van Zijl AJM. Management policies and prognosis in unstable angina pectoris. Use of coronary angiography in different practice settings. Erasmus University Rotterdam. Thesis 1992.

[24] Biagini A, Mazzei MG, Carpeggiani C *et al.* Vasospastic ischemic mechanism of frequent asymptomatic transient ST-T changes during continuous electrocardiographic monitoring in selected unstable angina patients. Am Heart J 1982; 103: 13–20.

[25] Amanullah AM, Lindvall K. Prevalence and significance of transient — predominantly asymptomatic — myocardial ischemia on Holter monitoring in unstable angina pectoris, and correlation with exercise test and Thallium-201 myocardial perfusion imaging. Am J Cardiol 1993; 72: 144–8.

Appendix

Participating clinics and collaborators: Thoraxcenter, Erasmus University and University Hospital Dijkzigt, Rotterdam, The Netherlands: *M. L. Simoons*; Department of Cardiology, Havenziekenhuis, Rotterdam, The Netherlands: *C. Leenders*; Department of Cardiology, Medisch Spectrum Twente, Enschede, The Netherlands: *J. Poortermans*; Department of Cardiology, Zuiderziekenhuis, Rotterdam, The Netherlands: *W. Remme*; Department of Cardiology, St. Clara Ziekenhuis, Rotterdam, The Netherlands: *M. Scheffer*; Department of Cardiology, Schieland Ziekenhuis, Schiedam, The Netherlands: *H. Werner*; Department of Cardiology, Ziekenhuis Hilversum, Hilversum, The Netherlands: *P. de Milliano*; Department of Cardiology, Medisch Centrum Alkmaar, Alkmaar, The Netherlands:

V. Umans; Department of Cardiology, Spaarne Ziekenhuis, Heemstede, The Netherlands: *E. Müller*; Department of Cardiology, Ikazia Ziekenhuis, Rotterdam, The Netherlands: *J. Kerker*; Department of Cardiology, Wilhelmina Ziekenhuis, Assen, The Netherlands: *M. de Leeuw*; Department of Cardiology, Reinier de Graaf Gasthuis, Delft, The Netherlands: *A. Withagen*; Department of Cardiology, Holy-Ziekenhuis, Vlaardingen, The Netherlands: *R. van der Heyden*; Department of Cardiology, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands: *R. Breedveld*; Department of Cardiology, Diakonessenhuis, Utrecht, The Netherlands: *J. Hartog*; Department of Cardiology, Maasziekenhuis, Boxmeer, The Netherlands: *M. Smits*; Department of Cardiology, Beatrixziekenhuis, Winterswijk, The Netherlands: *J. Stevens*; Department of Cardiology, Juliana Ziekenhuis, Apeldoorn, The Netherlands: *E. Faber*; Core laboratory for continuous ECG monitoring (Mortara) analysis, Cardialysis B.V., Rotterdam, The Netherlands: *P. Klootwijk, A. Spierings*; Data processing center Cardialysis B.V., Rotterdam, The Netherlands: *T. Lenderink, W. Groothuis, I. v. Oosterom, G. A. v. Es.*

Supported by grants from Eli Lilly and Company (Indianapolis, Indiana, U.S.A.).