Continuous Digital 12-Lead ST-Segment Monitoring in Acute Myocardial Infarction

CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

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Continuous Digital 12-Lead ST-Segtment Monitoring in Acute Myocardial Infarction / Rolf F. Veldkamp. - Delft : Eburon
Proefschrift Erasmus Universiteit Rotterdam. - Met lit. opg. -
Met samenvatting in het Nederlands.
ISBN 90-5166-451-6
NUGI 741
Trefw.: myocard infarct

Uitgeverij Eburon
Postbus 2867
2601 CW Delft

ISBN 90-5166-451-6

Continuous Digital 12-Lead ST-Segment Monitoring in Acute Myocardial Infarction

Continue digitale 12-afleidingen ST-segment bewaking tijdens het acute myocard infarct

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof. Dr. P.W.C. Akkermans M.S.
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 26 april 1995 om 15.45 uur

door

Rolf Frederik Veldkamp
geboren te Vleuten - De Meern

Promotiecommissie

Promotor	:	Prof. Dr. M.L. Simoons
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Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

To B.

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Chapter 1

Introduction

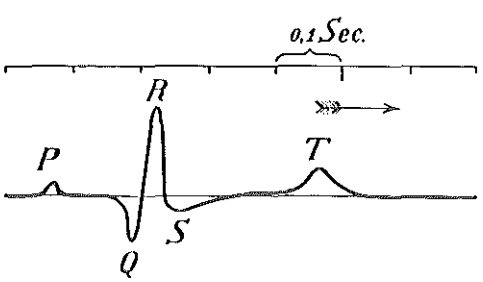
INTRODUCTION

HISTORY

In 1787 Aloysio Luigi Galvani (1737-1798), at that time Professor of Anatomy at the University of Bologna, demonstrated that the muscles of the hind limbs of a frog manifested "electromotive phenomena." A partly dissected frog's leg with a metal scalpel accidentally left in contact with an exposed nerve showed muscle contractions whenever a nearby electrostatic apparatus was rotated. Ensuing experiments led him to describe a method for stimulating tissues electrically by simply touching a muscle or nerve with two rods of dissimilar metals bound together, believing that it was due to electricity generated within the tissues. Allesandro Volta (1745-1827), Professor of Physics at the University of Pavia, challenged Galvani's interpretation by denying the existence of animal electricity, believing that the stimulation was due to electricity generated at the points of contact of the two metals. Thus arose a famous scientific controversy. To meet Volta's objection Galvani develo ped an experiment in which muscle contraction was induced using living tissue instead of metal rods. He showed that if a nerve was made to touch another tissue a two points, one injured and the other uninjured, the muscle supplied by the nerve would contract. This was the first unequivocal demonstration of the existence of electricity in living tissue and also the first description of the current of injury.[1]

Since then many researchers were "galvanized" by all kinds of electrical phenomena in various animal models, some of these related to the heart. With the development of more sensitive instruments more data became available, leading to a better understanding of the underlying physiology. In 1887 the London physiologist Augustus Désiré Waller (1856-1922) was the first person to record electrical activity of the human heart from the intact chest wall with the capillary electrometer.[2] Dissatisfied with the quality of the recordings obtained with this insensitive instrument, the Dutch physician and professor of physiology at the University of Leiden Willem Einthoven (1860-1927) developed a more sensitive string galvanometer,[3,4] enabling very sensitive and highly reproducible recordings of the electrical activi-

Figure 1



The serial repetitious deflections or waves denoted as P, Q, R, S, and T by Willem Einthoven. *Reproduced from Einthoven W.: Die galvanometrische Registrirung des menschlichen Elektrokardiogramms, zugleich eine Beurtheilung der Anwendung des Capillar-Elektrometers in der Physiologie. Archiv für die gesammte Physiologie der Menschen und der Thiere 1903; 472-80.*

ties of the heart. He introduced the term electrocardiogram (EKG or ECG), and labeled the serial repetitious deflections or waves as P, Q, R, S, and T. He was able to relate variations in the electrocardiographic pattern with conditions such as premature contractions of the heart, blocks in the heart's conduction system, and heart enlargement due to valve dysfunction. Noting that the shapes of the deflections varied widely with the lead placement he proposed a standard lead system known as leads I, II, and III. For his discovery of the mechanism of the electrocardiogram he was awarded the Nobel prize for physiology and medicine in 1924.[5]

It was Fred H. Smith who in 1918 as a resident at the Columbia University in New York first demonstrated ST-segment elevation as a sign of coronary occlusion using coronary artery ligation in dogs as a model.[6] He was advised to do so by James B. Herrick of Chicago who would later publish the first electrocardiogram obtained during the clinical manifestations of myocardial infarction.[1,7] It is now generally believed that ST-segment elevation is the reflection of reversible transmural ischemia, reflecting the differences in resting potentials and depolarization pattern between the ischemic and the healthy myocardium.

PHYSIOLOGY

Figure 1 denotes the different deflections of an electrocardiogram during one cardiac cycle. The P wave reflects the electrical activation of the atria. The QRS complex represents the electrical activation of the ventricles. The segment between the QRS offset and the end of the T-wave is a reflection of the plateau phase of the action potentials of the ventricular myocardium and return to the electrical resting state, known as repolarization. The ST segment is the segment between the end of the QRS complex (known as J-point) and the beginning of the T-wave.

Two electrocardiophysiologic phenomena have been suggested to explain ST elevation during transmural ischemia (lack of oxygen) resulting from total coronary artery occlusion as commonly seen during acute myocardial infarction. During the resting phase of the cardiac cycle (diastole) healthy myocardial cells maintain a resting membrane potential of approximately -80 microvolts, while this resting potential is less for the ischemic cell. Thus, during ischemia a current ("current of injury") flows from the ischemic to the healthy myocardium during diastole, leading to a depression of the T-Q interval. These currents disappear during the Q-T segment in the electrocardiogram, when all ventricular tissue is depolarized. This is represented as ST-segment elevation relative to the T-P and P-Q intervals in the ECG.[8,9] Furthermore, during the activation phase of the myocardium (systole) ischemic cells do not depolarize as much as healthy cells and their repolarization occurs earlier. This results in a current from the healthy to the ischemic myocardium during systole, which is also reflected as ST elevation on the electrocardiogram.[9]

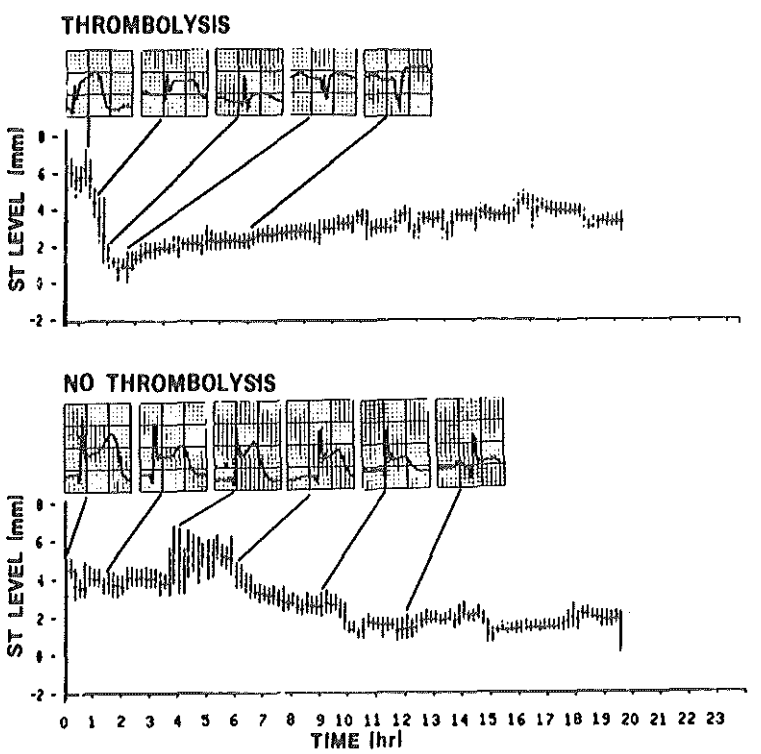
Approximately 75% of acute myocardial infarction patients have ST-changes suggesting transmural infarction at presentation (presumably new ST elevation or depression ≥ 1-2 mm), while this percentage may increase whith serial ECG assessments.[9-12] Patients without ST deviation generally have smaller infarcts and often have less benefit of reperfusion therapy.[12-17] Without reperfusion of the infarct related artery the ST deviation gradually lessens over the next hours to days due to necrosis of the myocytes and thereby loss of myocardial mass ("burn out").[11, 18-22] After reperfusion a more rapid normalization of the ST-

segment occurs. This phenomenon has been demonstrated clearly during intracoronary administration of thrombolytic drugs to dissolve the thrombus occluding the infarct related artery.[20-22] Figure 2 demonstrates the differences in ST-segment behavior over time during continuous coronary occlusion and after reperfusion through the infarct related coronary artery.

ST-SEGMENT MONITORING

The observation of rapid ST recovery at the moment of angiographically documented reperfusion led to several studies correlating quantitative ST recovery to infarct related artery patency. Several methods comparing ST-segment deviation between a post treatment ECG and a fixed pre-treatment reference ECG have been reported.[23-29] These methods measure the ST deviation in one or few post-treatment ECGs at intervals typically 60 to 180 minutes after onset of thrombolytic treatment. If the ST-segment has recovered below a threshold expressed as a percentage of the pre-treatment reference ECG ST level,

Figure 2



Holter ST-segment trends in 2 patients with complete occlusion of the infarct related artery. Top, successful reperfusion after intra-coronary thrombolysis is characterized by the sudden decline of ST-segment elevation. Bottom, unsuccessful reperfusion with a slow, gradual achievement of ST steady state. *Reproduced with permission from: Krucoff MW, Green CE, Satler LF, Miller KM, Del Negro AA, Pearle DL, Fletcher RD, Rackley CE: Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. Am J Cardiol 1986; 57: 916-22.*

reperfusion is considered to have occurred. If the ST-segment did not recover below this threshold reperfusion is considered to have failed.

Continuous ST-segment monitoring using Holter recorders was developed to better document the timing of reperfusion. Recordings were analyzed retrospectively and allowed to distinguish patients with reperfused infarct related arteries from those in whom the infarct related artery failed to reperfuse after treatment.[22] However, Holter recordings are limited in the number of leads to be used and cannot be used at the bedside for guidance of clinical care since they require off-line analysis. Therefore dedicated continuous multi-lead computerized electrocardiographs have been developed by several groups wich can measure, compare, and display the ST-segment in real time so that the recorded information can be used to guide clinical care.[30-35] The major application of these devices is the display of ST-segment recovery and of new ST-segment abnormalities as a reflection of ischemia in various unstable coronary syndromes such as acute myocardial infarction, unstable angina pectoris, and post coronary angioplasty. Accordingly they have been called "ST monitors" or "ischemia monitors."

THIS THESIS

The Ischemia Monitoring Laboratory at the Duke University Medical Center in Durham, USA, in cooperation with Mortara Instrument, Milwaukee, developed a real-time oriented digital 12-lead electrocardiograph. Essentials of this ST monitor (ST100) have been published previously.[34, 35] The manuscripts gathered in this thesis are a reflection of investigations as a research fellow in cardiovascular medicine at the Duke University Medical Center, focussing on the development and testing of hardware and software as well as the clinical application of ST monitoring.

Chapter 2 describes the initial experience of non-invasive patency assessment using continuously updated 12-lead ST-segment recovery analysis.[36] In a series of 22 acute myocardial infarction patients sensitivity for an occluded infarct related artery was 90% and specificity was 92%. In view of these promising results and the results of a larger 144 patient series,[37] an inter- and intra- observer variability analysis of this patency assesment technique was performed, as presented in Chapter 3.[38] The evolution and salient principles of an automated ST-segment analysis program for real-time non-invasive patency assessment is described in Chapter 4 and the results of the testing of this program during PTCA are presented in Chapter 5.[39, 40] In Chapter 6 patterns of ST deviation as seen on the 12-lead ECG during occlusion of the infarct related artery are correlated with the angiographically determined infarct related artery.[41] The possibility and limitations of a restricted lead set for ST monitoring for infarct related artery patency assessment are discussed. The prospects of ST-segment recovery as an endpoint in acute myocardial infarction trials are addressed in Chapter 7.[42] Chapter 8 characterizes the impact of coronary angioplasty Perfusion Balloon Catheters (PBC) as compared to standard angioplasty balloons on quantitative electrocardiographic parameters of ischemia severity, extent, and "burden." [43] A comparison of continuous ST-segment recovery analysis with methods using static electrocardiograms for noninvasive patency assessment during acute myocardial infarction is presented in Chapter 9.[44] Chapter 10 reviews ST monitoring applications during acute myocardial infarctions and compares it with other noninvasive patency assessment techniques. Other applications of the

ST monitor are discussed and areas for future research are outlined. Finally, the results presented in this thesis are summarized.

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Chapter 2

Continuously Updated 12-Lead ST-Segment Recovery Analysis for Myocardial Infarct Artery Patency Assessment and Its Correlation with Multiple Simultaneous Early Angiographic Observations

Continuously Updated 12-Lead ST-Segment Recovery Analysis for Myocardial Infarct Artery Patency Assessment and Its Correlation with Multiple Simultaneous Early Angiographic Observations

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Early angiography may not adequately subgroup patients with myocardial infarction if cyclic changes in coronary flow occur frequently. From a pilot experience using a new 12-lead ST-segment monitor, a continuously updated, self-referenced ST-recovery analysis method was developed to quantify both instantaneous recovery, as a noninvasive marker of patency, and cumulative ST recovery over time, as a marker of the speed, stability and duration of reperfusion. In 22 patients with acute infarction in whom 44 observations of unique angiographic patency were noted within 6 hours of presentation, serial patency assessments simultaneous with all angiographic observations predicted coronary occlusion with 90% sensitivity and 92% specificity. Of the 22 patients, 11 (50%) had multiple ST trend transitions suggesting cyclic changes in coronary flow before catheterization. Speed, stability and duration of ST-segment recovery were defined by the time to first 50% ST recovery, total number of ST-trend transitions and patent physiology index (percentage of monitoring period showing ST recovery), respectively. Subgrouped angiographically, the median (interquartile range) for cumulative ST parameters with patent (n = 8) versus occluded (n = 14) arteries were, respectively — time to 50% recovery, 1.57 (1.16, 1.70) versus 0.17 (−0.47, 0.32) hours; number of reelevation/recovery events, 1.5 (1, 3) versus 3 (1, 3); and patent physiology index, 52 (47, 59) versus 50 (5, 73). Thus, continuous ST-segment recovery analysis appears to predict simultaneous angiographic patency over serial assessments, whereas cumulative parameters appear to contain independent information, probably because of patency changes before or after angiography. (Am J Cardiol 1993;71:145–151)

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Angiographically defined patency provides only a brief anatomic visualization of the infarct artery during the course of ongoing infarction. More prolonged angiography has shown that cyclic or "unstable" infarct artery patency is common and consistently related to dynamic ST-segment changes.[1,2] Quantification of the ST-segment recovery process may provide both an instantaneous method for serial patency assessments and a cumulative measure of the speed and stability of reperfusion. Analytic methods for ST analysis in patients presenting with abnormal ST levels subject to sudden marked changes are limited.[3–7] To address this need, we developed a method of self-referenced, continuously updated ST-segment recovery analysis paired with a new 12-lead digital ST monitor and examined its performance in patients who underwent acute angiography during myocardial infarction. The goal of this retrospective analysis was to examine, in a preliminary fashion, the relation of ST-recovery analysis to simultaneous infarct artery patency and the relation of cumulative ST recovery reflecting speed, stability and duration of reperfusion to acute angiographic patency.

METHODS

Patient selection: All patients presented with chest pain within 6 hours and ST-segment elevation not reversed with nitrates, as previously detailed.[8] All patients had myocardial infarction by enzyme elevation and all underwent cardiac catheterization within 6 hours of admission. Choice of therapy and timing of catheterization were determined either through physician judgment or through the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 5 protocol.[9] ST-segment monitoring data were not accessible to the bedside caretakers in any case.

Angiographic analysis: For this analysis the infarct artery was defined as patent with Thrombolysis in Myocardial Infarction (TIMI) trial 2 to 3 flow, or as occluded with TIMI trial 0 to 1 flow. Unique angiographic observations were included for every patient in whom patency change (from patent to occluded or vice versa) occurred during catheterization, either spontaneously or as a result of further therapy. TIMI flow was determined by experienced angiographers (non-TAMI patients) or by the TAMI Angiographic Core Laboratory at the University of Michigan (TAMI 5 patients). In all cases

angiographic interpretation was made with no knowledge of ST-recovery data.

ST-segment monitoring: The Mortara ST Monitoring System (Mortara Instrument, Milwaukee) has been described in detail previously.[3,4,8] In brief, the device meets American Heart Association criteria for frequency response and sampling rate in standard electrocardiographic carts.[10] A 12-lead electrocardiogram is automatically acquired every 17 seconds, digitized and immediately compared with the patient's own baseline electrocardiogram for ST-segment changes over time in any lead(s). All measurements derive from median beats at J+60 ms. For the pilot experience, all clinical alarms were disabled. In all patients ST monitoring was initiated with impedance-monitored skin preparation (Quik Prep, Quinton Medical, Seattle, Washington) using radiolucent lead wires and electrodes. A total of 10 electrodes were placed over the standard 6 precordial positions, with the 4 limb leads placed on the bony clavicles and iliac crests ("monitoring position") to stabilize baseline. Lead positions remained fixed throughout the monitoring period. Monitoring was initiated before or as

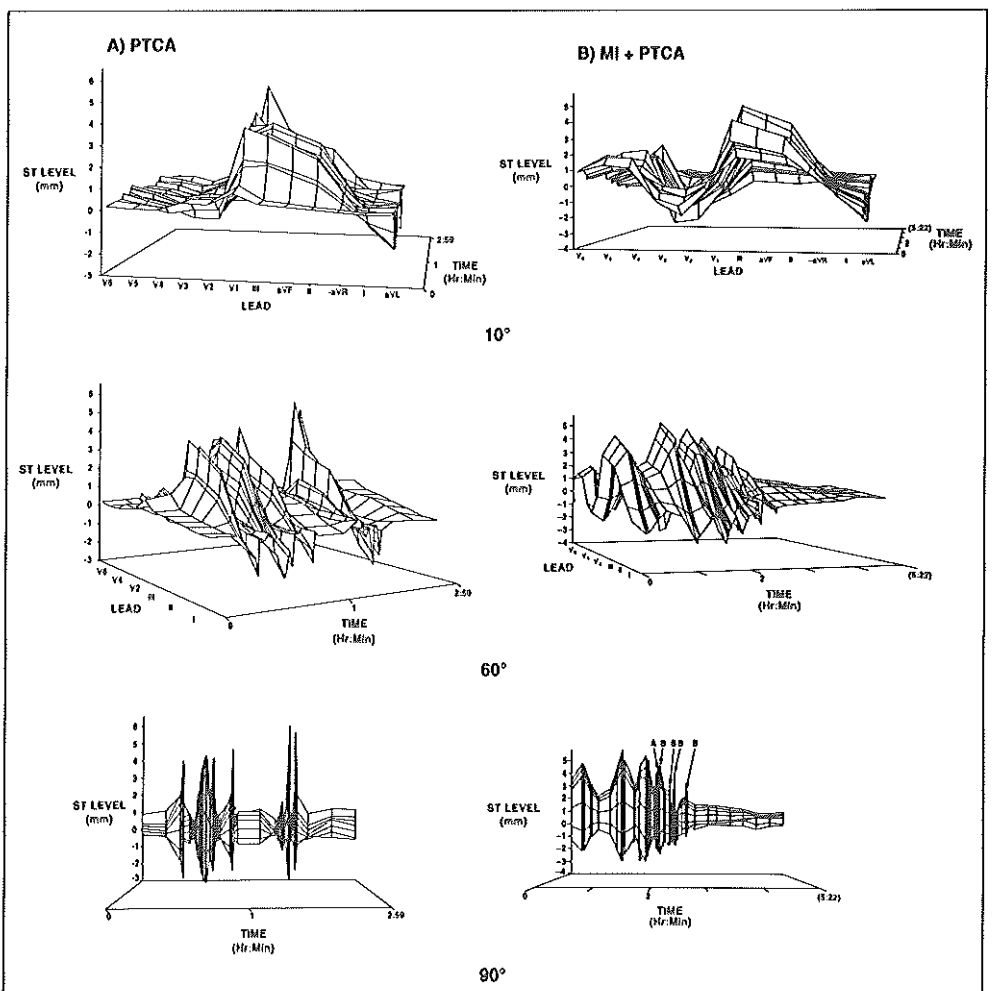

FIGURE 1. Three-dimensional graphic display of digital 12-lead ST-segment data trended as ST level *(Y-axis)* over each of the 12 standard electrocardiographic leads *(X-axis)*, over time *(Z-axis)*, shown in 3 spatial rotations (10°, 60°, 90° from *top to bottom*) for each of 2 patients. *A*, during elective percutaneous transluminal coronary angioplasty (PTCA) of the right coronary patterns from 7 balloon inflations create 7 episodes of ST (re-)elevation in identical precordial "fingerprint" pattern followed by ST recovery with each balloon deflation. The "peak and trough" pattern of transitions over time is the paradigm for reperfusion/reocclusion. *B*, same graphic display in a patient with inferior infarction treated with primary angioplasty. Multiple ST transitions in matched fingerprint pattern occur spontaneously for over 2 hours before initial angiography *(A)*, which revealed an occluded right coronary, reperfused by emergency balloon inflations *(B)*. MI = myocardial infarction.

soon after the onset of therapy as possible. Exclusions from our retrospective analysis included hookup of the ST monitor >60 minutes after onset of therapy or interruption of the ST information by persistent noise, bundle branch block, ventricular rhythm or ventricular pacemaker. All patients were kept at bed rest.

ST-recovery scanning and analysis technique:* All stored electrocardiographic data were downloaded to a personal computer and analyzed with custom-written scanning software which we have previously described.[3] All studies were analyzed over the first 6 hours, including the time of angiography. Patterns of ST recovery and reelevation associated with cyclic flow changes were derived from previous experience with angioplasty balloon inflation and deflation.[4,11–13] Similarities are graphically illustrated in Figure 1. The absence of a predefined "baseline" in the myocardial infarction presentations, however, mandated modifications for quantitative measurements.

The 3-dimensional graphic display in the scanning software illustrated in Figure 1 was used to define each patient's ST measurement matrix. The measurement matrix was taken as the single most abnormal lead in the most abnormal electrocardiogram unless the lead location changed over the course of monitoring or multiple precordial zones (where anterior zone = V_1–V_4; low lateral zone = V_5–V_6; high lateral zone = I, aVL; and inferior zone = II, III and aVF) showed ST elevation simultaneously. With either of these exceptions, the measurement matrix was taken as the summated absolute deviation over the entire 12 leads. Graphic display was also used to identify each patient's multilead pattern of ST activity, or ST "fingerprint."[13] Episodes of recurrent ST deviation were taken as evidence of infarct artery reocclusion only when the fingerprint pattern recurred.[13]

Quality control of the ST matrix and graphic displays was afforded by full disclosure 12-lead superimposition scanning within the analysis software. Every standard 12-lead electrocardiogram was directly visualized in the Duke Ischemia Monitoring Core Laboratory for all studies.

Analysis of ST recovery centered on definition of "troughs" and "peaks" in the trend of the ST-matrix level over time (Figure 2). Troughs and peaks represented points of transition from ST recovery to worsening or from worsening to recovery, respectively. A transition peak was defined as the most abnormal ST level directly preceding any single period of ST-segment recovery. ST-segment recovery was defined as resolution within a 3-hour period consisting of either (1) ≥50% recovery from the immediately preceding peak ST level

*See Appendix for summary of definitions.

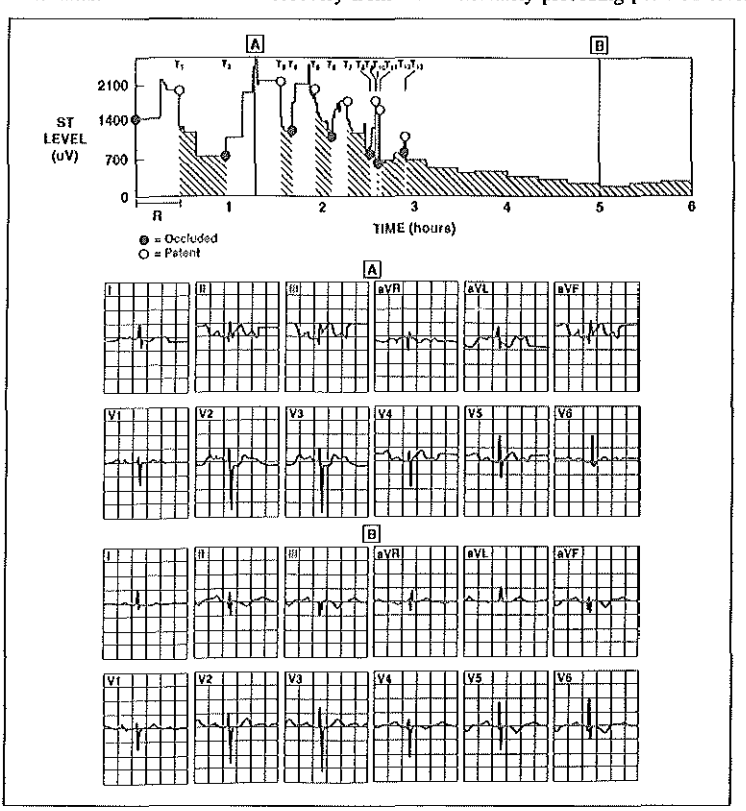

FIGURE 2. Two-dimensional ST-matrix trend from patient in Figure 1B. Time from onset of monitoring to first ST recovery is shown as the interval R. Transition points (T_1 to T_{13}) associated with peaks and troughs are identified as changes from ST recovery to reelevation or vice versa. Patent physiology index equals the sum of the duration of the *shaded* recovery intervals divided by the entire monitoring period. All trend points represent standard 12-lead electrocardiographic information, as illustrated below the trend, which is confirmed using superimposition scanning.

or (2) 35 to 49% recovery relative to the immediately preceding transition peak; and ≥50% recovery relative to the most abnormal peak documented at any time in the study before the current electrocardiogram. The current electrocardiogram was defined as the electrocardiogram corresponding to each moment an ST-recovery analysis was performed.

A transition trough was defined as the most normalized ST level preceding any single period of ST-segment reelevation. ST-segment reelevation was defined as reelevation in a matched precordial "fingerprint,"[13] evolving over ≤60 minutes and lasting for ≥60 seconds. Minimal amplitude of reelevation was required to be ≥150 μV in any 2 leads or ≥200 μV in a single lead or to a level equal to or greater than the level of the most recent transition peak.

Recovery intervals were defined as beginning at the moment of 50% ST recovery and ending at the onset of reelevation. The time to first 50% ST recovery was defined as the time from the onset of therapy to the onset of the first recovery interval up to a maximum of 6 hours if no such recovery occurred within the monitoring period. The patent physiology index was taken as the percentage of the monitoring period showing ST recovery, defined as the summated duration of all recovery intervals divided by the total monitoring duration × 100. The total number of peaks and troughs from the onset of monitoring to the first contrast injection was taken as the "number of transitions."

Patency assessment at the moment of angiography: Periods of ST recovery were interpreted as the result of reperfusion and periods of persistent (or re-)elevation were interpreted as the result of (re-)occlusion. Periods of incomplete ST transition were interpreted as indeterminate patency. In all patients, an ST-recovery analysis patency prediction was logged simultaneously with the first contrast injection of the infarct artery. In all patients with subsequent unique angiographic observations (as previously defined), additional ST-recovery predictions were logged at each of those times.

Statistical methods: All categorical data are reported as n (%). Because many of the continuous variables are not normally distributed, they are reported as 50th (mean 25th, 75th) percentiles. Ranges are often also included. Only descriptive data are reported, and no statistical tests were performed.

RESULTS

All 22 patients from our pilot experience meeting the criteria were analyzed for this report. The infarct artery was the left anterior descending in 12, the circumflex in 2, and the right coronary artery in 8. Acute therapy consisted of only thrombolytic drugs in 10, only angioplasty in 2, and both in 10. Median time from chest pain onset to initiation of ST monitoring was 4.3 (2.9, 7.6) hours. Median time from ST monitoring to onset of acute therapy was –0.8 (–1.8, 0.3) hours.

At the first contrast injection the infarct artery was patent in 8 (36%) and occluded in 14 (64%) patients. At least 1 period of ST recovery was seen before angiography in 8 patients (100%) with patent arteries, and in 11 (79%) with occluded vessels. More than 2 transitions to reelevation or recovery were seen before catheterization in 3 patients (38%) with patent arteries, and in 8 (57%) with occluded vessels. The 50th, 25th and 75th percentiles, and ranges for time to first 50% ST recovery, the number of transitions over the monitoring period, and patent physiology index in patients with patent versus occluded arteries are shown in Figure 3. Patients with angiographically occluded vessels had a somewhat shorter time interval from onset of therapy to some evidence of transient reperfusion than did patients with

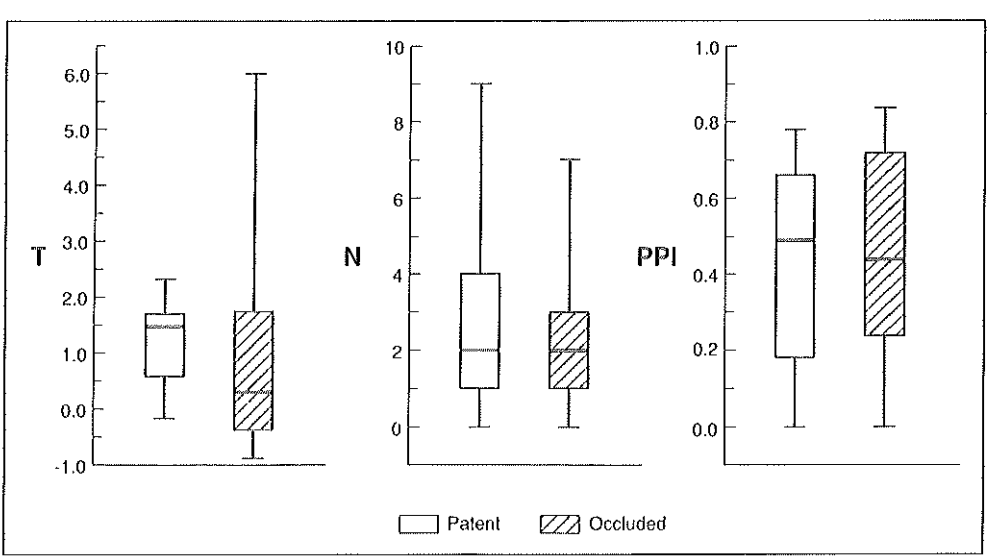

FIGURE 3. Range, 50th, 25th and 75th percentile values of time to first ST recovery (T), number of trend transitions (N), and patent physiology index (PPI) shown subgrouped by coronary patency status at initial angiography.

patent vessels. The stability of reperfusion and duration of reperfusion physiology over the 6 hours monitored were similar whether the initial angiogram showed a patent vessel or an occluded one.

In all 22 patients, <50% ST recovery or ST reelevation was 100% sensitive and specific for simultaneous angiographic occlusion on first contrast injection. Of the 44 angiographically documented patency changes in these 22 patients, sensitivity and specificity for angiographic occlusion were 90 and 92%, respectively.

In 16 of our 22 patients, ST-segment monitoring was initiated before therapy. Of these 16 patients, ST-segment recovery occurred at least once before therapy (suggesting spontaneous reperfusion) in 5 (31%) (Figure 1B).

DISCUSSION

The major findings of this study are twofold. First, serial instantaneous assessments of ST-segment recovery using continuously updated reference points appears to predict simultaneous infarct artery patency, even over multiple changes of patency. Second, patency defined acutely by a single angiographic procedure does not appear to correlate with the rate, stability and duration of ST recovery quantified cumulatively over time periods broader than the catheterization itself. We interpret these findings to indicate that unstable ST-segment recovery reflects cyclic flow changes in the infarct vessel that may occur before, during or after the brief period of time documented by angiography. In our study group, 50% of patients exhibited ST-segment evidence of cyclic flow before catheterization. The incidence of this observation is similar across all 5 other studies that have used continuous electrocardiographic monitoring early in myocardial infarction.[1,2,5–7] Of our 16 patients in whom ST monitoring was begun before therapy, 31% showed evidence of spontaneous reperfusion, similar to our findings in previous work.[11] This spontaneous behavior suggests

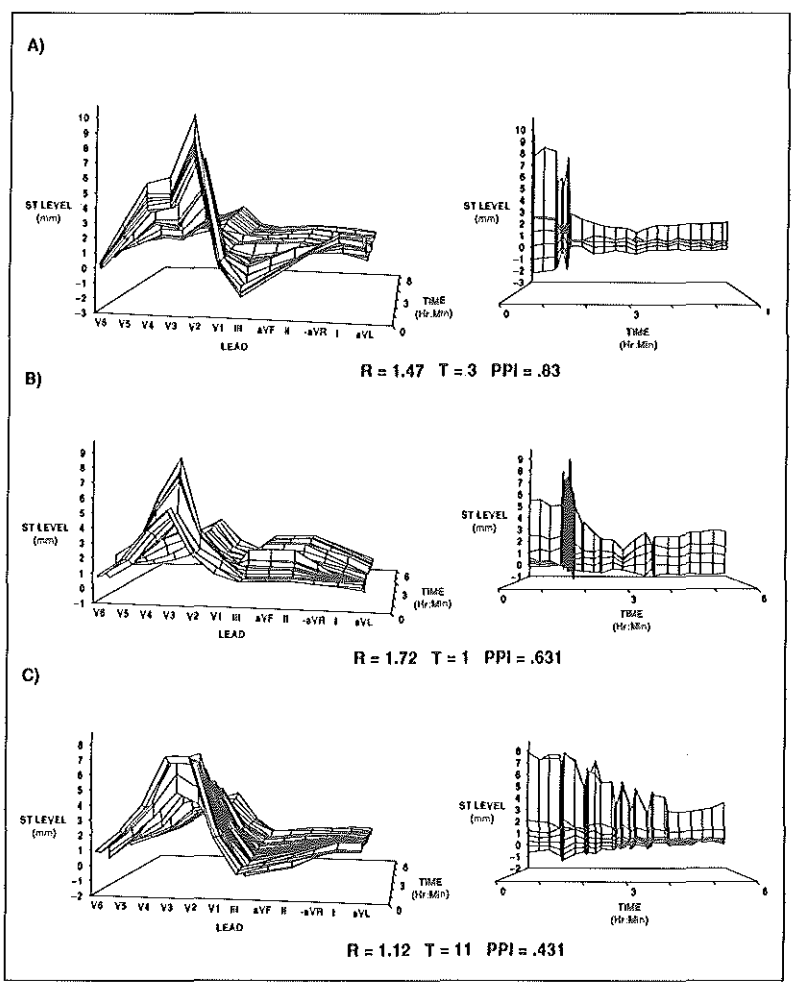

FIGURE 4. ST-monitor data from 3 patients *(A to C)*, all of whom had patent left anterior descending coronary arteries at initial catheterization, shown in same format as Figure 1. Time to first ST-segment recovery (R), the number of transitions (T) and the patent physiology index (PPI) are shown for each patient. See text for discussion.

that cyclic flow changes may not result from therapy, but rather may be the underlying pathophysiology of early infarction on which therapy is superimposed.

It has previously been suggested that cyclic changes in infarct artery patency may have functional importance.[2] Correlations of slow or unstable ST-segment recovery with poor regional wall motion, larger enzymatic infarct size, and poor clinical patient outcome and survival[6,14–17] have been reported. None of these reports, however, have detailed quantitative parameters for cumulative ST recovery over time. The ramifications of such a method are illustrated in Figure 4. In a multifactorial trial design comparing thrombolytic regimens using acute angiographic patency and correlating acute patency to predischarge left ventricular function,[9] all 3 patients in Figure 4 were described as having patent left anterior descending infarct arteries. However, ST-recovery patterns suggest different rates, stability and duration of reperfusion within this "homogenous" angiographic group (Figure 4). The patient in Figure 4A shows early cyclic flow changes and early stable reperfusion. The patient in Figure 4B shows persistent occlusion until just before angiography, with stable reperfusion thereafter. The patient in Figure 4C shows the earliest evidence of reperfusion, but with ongoing cyclic flow changes and very low duration of patency over a 4-hour period before and after angiography. As our pilot data suggest, quantification of cumulative ST recovery over time with parameters reflecting the speed, stability and duration of reperfusion may provide an independent physiologic context for the interpretation of acute angiographic anatomy.

The data we report represent a pilot experience acquired while familiarizing community and university hospitals with the use of 12-lead ST monitors. These data do not represent a prospective or formally blinded analysis, a consecutive patient population, or a sample size large enough to draw rigorous conclusions about the accuracy of the method for real-time patency prediction. Acute angiography was performed by protocol in some and by clinical selection in others. No functional outcome or left ventricular function data were analyzed, so inferences about ST recovery and functional outcome remain unproven.

Despite these limitations, the implications of the method and the pilot results are no less intriguing. Angiographically homogenous subgroups appear to be physiologically heterogenous as quantified by continuous ST-recovery analysis. Seventy-nine percent of our patients with occluded vessels at angiography had at least 1 episode of ST recovery before catheterization, suggesting transient reperfusion. The time to first evidence of reperfusion was somewhat earlier in patients with angiographically occluded vessels than in those with patent arteries. Even our limited data show unequivocally how vulnerable a single angiographic assessment may be to "undersampling" a dynamic phenomenon such as an ongoing myocardial infarction. Determination of the actual additional information content provided by quantification of continuous ST-segment recovery must await a proper prospective trial design in a suitable number of patients. Such research is currently underway.

Serial instantaneous patency assessments based on ST-segment recovery analysis also have clinical management and investigational potential. Current technology makes 12-lead ST-segment monitoring with a portable device feasible in small community hospitals as well as during transport between hospitals, as was frequently done in this pilot. Thus, unlike angiography, ST-segment monitoring can be initiated from the onset of therapy, and can be continued for as long as the patient is at bed rest. Triage of patients given thrombolytic therapy to aggressive or conservative therapeutic strategies could be better studied and managed with a continuous noninvasive marker of failed or unstable reperfusion that was accurate over serial assessments in real time. A prospective, blinded experience including acute catheterization by protocol in a larger patient population is currently being analyzed to better assess the method's performance in this respect.

Thus, this pilot experience demonstrates that continuous 12-lead ST-segment monitoring can be initiated in a timely and practical fashion using currently available technology. Paired with our method of ST-segment recovery analysis using self-referenced, continuously updated measurements, both real time and retrospective determination of the speed and stability of reperfusion appear likely to provide unique and useful information for both investigational and clinical purposes. More rigorous assessment of this potential must await further study.

Acknowledgment: We thank Joseph C. Greenfield, Jr., MD, for his support and guidance in this work and this manuscript, and Ruth G. Wagoner for her invaluable assistance in the final preparation of this paper.

APPENDIX: SUMMARY OF ST-MEASUREMENT AND PARAMETER DEFINITIONS

ST-measurement matrix (trend): (1) the most abnormal single lead from the maximally abnormal electrocardiogram (default), or (2) summated deviation (sum of absolute differences per lead) if either (A) the single most abnormal lead designation changes across ≥2 leads, or (B) there are ≥2 precordial zones show ST elevation.

Transition points: TRANSITION PEAK: the most abnormal electrocardiogram immediately preceding a period of ≥50% ST-segment recovery.

TRANSITION TROUGH: the most normalized electrocardiogram immediately preceding a period of ST reelevation.

ST-segment recovery and reelevation: ST-SEGMENT RECOVERY: (1) resolution of ≥50% of the immediately previous transition peak, or 35 to 49% of the immediately previous transition peak and ≥50% of the most abnormal matrix level over the entire recording period up to the current electrocardiogram, and (2) developing within 3-hour period.

ST-SEGMENT REELEVATION: (1) ST-reelevation developing within a 1-hour period; and (2) lasting >60 seconds; and (3) in matched "fingerprint" zone; and (4) 2

leads ≥150 μV each; or (5) 1 lead ≥200 μV or ≥ST level of immediately previous transition peak, whichever first.

ST-RECOVERY INTERVAL: the time from the first electrocardiogram achieving ST-segment recovery to the time of the first electrocardiogram achieving ST-segment reelevation.

Trend parameters: TIME TO FIRST EVIDENCE OF REPERFUSION: the time from the onset of lytic therapy to the onset of the first ST-segment recovery interval.

PATENT PHYSIOLOGY INDEX PERCENTAGE (PPI%): the sum of the duration of all ST-recovery intervals divided by the duration of the total recording period ×100.

NUMBER OF TRANSITIONS: the total number of transition peaks and troughs over the recording period.

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Chapter 3

Inter- and Intra-Observer Variability Performing Continuously Updated ST-Segment Recovery Analysis Following Thrombolytic Therapy for Myocardial Infarction

INTER- AND INTRA-OBSERVER VARIABILITY PERFORMING CONTINUOUSLY UPDATED ST-SEGMENT RECOVERY ANALYSIS FOLLOWING THROMBOLYTIC THERAPY FOR MYOCARDIAL INFARCTION

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ABSTRACT

BACKGROUND: Continuously updated 12-lead ST-segment recovery analysis for prediction of infarct artery patency depends on human interaction with a computerized review station. To test the variability of this method, 3 human operators analyzed a common group of infarction recordings following thrombolytic therapy.
METHODS: ST-segment recordings from 50 patients were used for inter-observer testing, and 30 were re-read for intra-observer testing. All were analyzed over both 90 and 360 minutes. Each reader identified all ST-segment trend transitions and logged a patency assessment at the end of each monitoring period. Kappa statistics were used for comparisons of all categorical and continuous variables, including comparison of each reader's assessment of each minute of each study. Concordance was described by Kappa values as: 0.85 - 1.0 = superior; 0.70 - 0.84 = excellent; 0.1 - 0.69 = poor to fair; 0.0 = random; -1.0 = discordance.
RESULTS: Dynamic ST-segment re-elevation with ≥ 2 transitions occurred in 20 - 30% of studies, and 81 - 100% were interpreted as patent at the end of the 90 and 360 minute periods. Over the first 90 minutes, both intra- and inter-observer concordance for both categorical and continuous variables was superior. Variability increased slightly for all variables when observations were carried out over 360 minutes, although concordance overall remained excellent to superior. Sources of variability included differences in interpretation of low ST amplitude / high noise ECGs, anterior ST-segment depression, and gaps in the data stream, as well as operator fatigue.
CONCLUSION: Continuously updated 12-lead ST-segment recovery analysis can be learned to a high level of intra- and inter- observer consistency.

INTRODUCTION

Continuously updated ST segment recovery analysis has been developed for real-time evaluation of coronary patency in patients given thrombolytic therapy for acute myocardial infarction.[1,2] In the hands of an experienced interpreter, ST-segment recovery analysis has been shown to identify simultaneous angiographic coronary occlusion more accurately than other bedside clinical descriptors.[2] As a conti-

nuous objective marker, ST-segment recovery analysis can quantify both the speed and stability of reperfusion, providing a unique method for the evaluation of thrombolytic regimens.

As a computer-assisted method, patency assessment with ST-segment recovery analysis remains dependent on the human operator interacting with the program. The human operator combines a structured set of quantitative rules[1] with more qualitative judgements to accomplish this interaction. Interpretative determination of reperfusion or re-occlusion and the timing of reperfusion or subsequent re-occlusion could be grossly affected if differences in judgement among operators were significant, frequent, or accumulated over the time interval monitored.

To test the inter- and intra-observer variability of this technique, 3 human operators of varying experience performed ST-segment recovery analyses on a cohort of patient studies over 2 time intervals in a prospective trial design, including blinded repeat analysis of over half the studies by each operator. Differences within and between operators in all patency interpretations over every minute of every study were assessed.

METHODS

Patient studies

ST-segment monitor studies were selected from a recently completed acute myocardial infarction (TAMI 9) trial.[3] Inclusion criteria for that trial included: onset of chest pain within 6 hours of presentation; diagnostic ST elevation or anterior ST depression suggesting posterior infarction of > 200 μV not reversed by sublingual nitroglycerin; and no contra-indication to thrombolytic therapy. All patients were treated with tissue plas-minogen activator (rt-PA), systemic heparin, and aspirin. Patients also received systemic perfluorocarbon in 50% of cases. For the purposes of our investigation, the first 50 studies retrospectively identified with the following characteristics were selected: ST monitoring begun at or before the administration of thrombolytic therapy and continued for at least 6 hours; normal QRS conduction at the onset of monitoring; no ST monitor technical failure of > 1 hour out of the first 6 hours of monitoring. No other technical factors, including study noise level, dynamic ST-segment behavior, peak ST-segment level, or infarct location, were used to bias study selection.

ST-Segment Monitoring and Study Preparation

Our technique of 12-lead continuous ST-segment monitoring has been previously described in detail.[1,2,4] Modified limb lead positions and impedance-metered skin preparation were used in all cases, as we have described.[1,4] The Mortara ST-Segment Monitor (Mortara Instrument, Milwaukee) is a digital 12-lead ECG monitor that meets fidelity criteria for standard ECG carts.[5] In all cases the device was programmed to acquire and store a 12-lead ECG every 20 minutes. In addition to this mandatory minimum storage interval, "surveillance" of ST levels over all 12 leads was performed automatically every 17-20 seconds. With any change from each patient's own baseline of > 100 μV in any 2 leads or > 200 μV in any 1 lead that persisted or worsened for > 60 seconds, additional ECGs were stored every 30 seconds over a 3 minute period.

All data from each ST monitor study were downloaded to a floppy disc as a digital data stream. Prior to distribution to the operators, two electronic "marks" were imbedded into each patient's data stream: one at the ECG acquired 90 minutes following onset of thrombolytic therapy and

one at the ECG acquired 6 hours following onset of thrombolytic therapy. The electronic marks prevented the operator from seeing any further ECG information beyond the marked ECG, thus preventing any interpretative bias by "future" information. This blinding procedure was identical to that used in the TAMI 7 ST-segment analysis.[2]

Of the 50 studies selected, 30 were randomly selected for re-reading to generate intra-observer comparisons. The 80 total studies thus prepared for analysis (50 studies and 30 re-reads) were sequenced in random lots of 10 uniquely for each operator, with attention to avoiding re-reads in close proximity to one another by a single operator.

For each study each operator received a folder which contained the hard copy ECG that originally qualified the patient for thrombolytic therapy, the time of onset of chest pain, the time of onset of thrombolytic therapy, and a "marked" floppy disk containing the ECG data. Operators were blinded to all other clinical data. In each patient, analysis was completed first up to the 90 minute mark, then up to the 6 hour mark, in sequence. The results of each 90 minute analysis was logged on a computerized data entry screen. This system then stored these responses in a file, unretrievable by the operators, before the six hour interpretation began. This method was used to prevent any editing of the 90 minute responses during completion of the 6 hour analyses.

ST-SEGMENT RECOVERY ANALYSIS

Method and Training Level

Our method of ST-segment recovery analysis using this program has been described in detail.[1] In brief, there are two stages in the process. First, a matrix of ST measurement is selected for use as a trend over time. As guided by published rules[1] the measurement matrix may be either a trend of the most abnormal single lead over time or a trend of summated ST deviation over all 12 leads. Once the matrix is determined, transition points or "peaks" and "troughs" within the trend of the matrix ST level over time are identified and used to demarcate the monitoring period into intervals of ST "recovery" or "re-elevation."[1] ST recovery intervals are interpreted as the result of a patent infarct artery. ST re-elevation intervals are interpreted as the result of an occluded infarct artery. If the "marked" ECG occurs during an apparent but incomplete ST transition, arterial patency is interpreted as indeterminate.

Operator training consisted of two parts. Conceptual underpinnings of the methodology were conveyed in didactic sessions. Experience was conveyed through individual and "classroom" exposure to acute infarction recordings from previous studies (none of which were included in the current study test set). At the time of the current study, it was estimated that the most experienced operator (Reader A) had over-read > 400 acute infarction recordings, the least experienced operator (Reader B) had overread < 50 such recordings, while the third operator, Reader C, was between these two.

Analytic Endpoints

The endpoints of interest were two-fold. For each study, the times of transition from patency to occlusion or vice versa were recorded, along with the patency assessment at the transition times. These measures were made during the first 90 minutes and during the subsequent 4.5 hours of monitoring. Secondly, patency was assessed at the time of initiation of monitoring, at the 90 minute marked ECG, and at the 6 hour marked ECG. Each patency assessment was considered a stable

definition of the patient's condition until a new transition point was identified, creating consistent intervals of patency or occlusion.[1] Therefore, a patient's patency status was definable over the entire 90 minute or 6 hour monitoring period for every minute within those periods.

Statistical Methods

The categorical endpoints of patency at 90 minutes, patency at 6 hours, number of transitions within the first 90 minutes, and number of transitions over the first 6 hours were analyzed using Kappa statistics. A Kappa of 1 implies total agreement. A Kappa of -1 implies perfect disagreement. A kappa of 0 implies random chance. For the purposes of this study, Kappa values of 0.85 - 1.0 were con-sidered superior concordance, values of 0.70 - 0.84 excellent concordance, values of 0.55 - 0.69 good concordance, and 0.1 - 0.54 poor to fair concordance.[6] "Conti-nuous" agreement over each of the 90 minute and 6 hour time periods was measured by first determining the patency decision for every minute within the time period of interest for a patient. The Kappa was then derived between observers for that patient across all 90 minutes and again across all 360 minutes. The intra-observer reliability across the time period of interest was calculated over the 30 patient studies as an average of the 30 Kappas. The inter-observer reliability across the time period of interest was calculated for each pair of observers over the 50 patient studies as an average of the 50 Kappas.

Following analysis of the data, the operators reviewed all discrepancies between any two readers in every patient. An open consensus was used to identify the source of each discrepancy. These characteristics were categorized into groupings according to common underlying principles of interpretation.

RESULTS

Intra-observer variation

All 3 operators completed each of 30 randomly selected studies up to both 90 minutes and 6 hours twice. As characterized by Reader A, these studies included 6 patients (20%) with ≥ 2 transitions at 90 minutes and 7 patients (23%) at 360 minutes, ranging overall from 0 to 9 transitions. At 90 minutes, 25 of the 30 studies were interpreted as patent, 5 as occluded and 0 as indeterminate. At 6 hours after thrombolytic therapy all 30 studies were interpreted as patent.

As shown in Table 1, there was perfect agreement within each of the 3 operators in both the total number of transitions and determination of patency at 90 minutes, with superior concordance over each of the 90 minutes within each patient's study. Slight deterioration of the intra-observer readings was seen at 360 minutes, particularly in the least experienced reader B. Overall however, concordance within each reader remained excellent.

Inter-observer variation

All 3 operators completed each of the 50 randomly sequenced studies up to both 90 minutes and 6 hours. As characterized by Reader A, after 90 minutes there were 13 patients with ≥ 2 transitions (26%), ranging from 0 to 6. At 90 minutes, 41 of the 50 studies were interpreted as patent, 9 as occluded, and 0 as indeterminate. After 6 hours there were 15 patients with ≥ 2 transitions (30%), ranging from 0 to 9. At 6 hours after onset of therapy, 48 studies were inter-preted as patent, 2 as occluded, and 0 as indeterminate.

The inter-observer variability for the categorical variables across all 3 operators and between each pair is also shown in Table 1. Agreement was excellent in both the prediction of patency and the number

of transitions. Although more reliability existed in the 90 minute assessments than at 6 hours, the level of agreement even out to 6 hours remained excellent.

Median Kappa statistics from comparisons of every 1 minute assessment over all 3 operators and for each pair over the 90 minute and the 6 hour monitoring periods are also shown in Table 1. As can be seen, the median Kappa was 1 in every comparison.

Table 1: Intra- and Inter-Observer Comparisons: Kappa Statistics

	# Transitions		Patency Assessment		Continuous*	
	90 min	6 hour	90 min	6 hour	90 min	6 hour
Reader(s):						
A vs. A	1.0	0.92	1.0	1.0	1.0	0.92
B vs. B	1.0	0.77	1.0	1/30 dis**	1.0	0.83
C vs. C	1.0	0.91	1.0	1/30 dis**	1.0	0.99
A vs. B	0.82	0.74	0.79	0.65	1.0	1.0
B vs. C	0.89	0.80	0.93	0.85	1.0	1.0
A vs. C	0.82	0.76	0.79	0.79	1.0	1.0
Overall inter-obs.	0.88	0.77	0.86	0.76	1.0	1.0

* Agreement as average of Kappa every minute over entire monitored

** No Kappa due to zero's in 2X2 tables.

Sources of Discrepancy

Of the 50 studies and 30 re-reads, each read over both 90 and 360 minute intervals, there were no examples of discrepancy in which all 3 operators disagreed. A total of 23 examples were identified in which 1 reader varied from the other two.

In 3 examples one operator deferred an interpretative conclusion until the next available ECG due to marginal noise levels, causing periods of 2 - 19 minutes of discrepancy. In 5 additional instances operators differed in judgements on wheher to include or exclude noisy ECGs that affected measurements sufficiently to change interpretations. In 4 of these 5 this judgement involved a single ECG that created a measurable transition point if included which was absent if the ECG was excluded. In the fifth example, a period of ECGs all with increased noise content were taken as an ST re-elevation event by 1 operator and as artifact by 2 operators. In all 5 instances judgements on noise rejection that affected clinical interpretation occurred during study periods when ST levels were low relative to the noise level itself.

In 7 cases the operator's decision on how to handle anterior ST depression led to some interpretative discrepancy. In 4 instances, one operator used 12-lead summated ST deviation for the ST-segment measurement matrix, interpreting the anterior ST depression as posterior injury current associated with inferior ST elevation, while 2 operators used the single most abnormal lead for the ST-segment matrix, taking the anterior ST changes as "reciprocal depression." In 2 instances

anterior ST depression either persisted or recurred after inferior ST elevation had resolved. One operator interpreted these as evidence of infarct vessel occlusion, while the other two considered them evidence of distant ischemia but not definitive re-occlusion. In 1 case, both inferior ST elevation and anterior ST depression resolved, however the anterior leads subsequently became grossly elevated. One operator took these changes as pathologic while two took them as nonspecific.

Discrepancies in 4 cases resulted from the operator's interpretation of a data gap. In all 4 cases, ST recovery of > 50% occurred during the interval between the hard-copy admission ECG and the first ECG of the monitored period (the interval during which the patient gave informed consent and was randomized into the TAMI protocol prior to being hooked up to the ST monitor). In all cases these changes preceded administration of thrombolytic therapy and the hard copy ECG represented the maximal ST levels compared to the ST-monitored portion of the study. Two operators interpreted patency at the onset of monitoring based on inclusion of the pre-monitoring hard copy ECG, while 1 interpreted the onset of ST monitoring as indeterminate.

In 4 cases discrepancies resulted from erroneous application of the pre-defined methodologic criteria[1] by the operator. In 3 instances 1 operator defined the ST-segment measurement matrix as the single most abnormal lead despite changes in the location of the peak ST levels over the course of the studies. In 1 case 1 operator interpreted a period of ST re-elevation as pathologic, although the ST amplitudes did not meet criteria for such.

DISCUSSION

With the ability to continuously characterize dynamic changes in real time, computer-assisted methodologies can enhance physiologic monitoring. The vulnerabilities of this direction in medical technology are twofold: in the ability to incorporate false assumptions into software; and in the variability of the human operators who interact with the programs. We have pursued the noninvasive detection of reperfusion and reocclusion using continuously updated 12-lead ST segment recovery analysis.[1, 2] We have previously shown that, in the hands of an experienced operator, the assumptions within this computer-assisted method correlate well with angiographically documented infarct artery patency.[1, 2] The data presented in our current study suggest human operators can learn this methodology to a high level of both intra- and inter-observer consistency.

It is important to note that "interpretations" of infarct artery "patency" or "occlusion" in this particular study were not correlated with any external "gold standard," as has been done previously.[1, 2] This trial design sought only to elucidate the amount and sources of intra- and inter-observer variability as different operators with different levels of experience applied our methods to the identical patient studies. It is also important to note that the operators were all didactically "trained" in the methodology in an effort to achieve the most consistent possible analyses, and so do not necessarily represent the capabilities of physicians without such training.

The dynamic behavior of ST segment levels early in infarction, the noise level inherent in many ECG recordings in acutely ill patients, and the operator's role combining quantitative "rules" with qualitative judgements were the focus of our trial design. The presence or absence of physiologically important events, the number, timing, onset and resolution of each event,

and the interpretation of each event relative to infarct artery patency were all tested in our trial design. Over the 450 hours of monitoring compared within each of the 3 operators, there was almost no intra-observer variability in any of the parameters assessed in any operator, although performance of the least experienced operator deteriorated somewhat more over the 6 hour periods. Over the 1,125 hours of monitoring compared across the 3 operators, inter-observer variability was strikingly small, again as evaluated over every parameter assessed. Again, there did appear to be a trend showing slightly greater variability in later periods (around 6 hours after thrombolytics) than in the very acute periods (90 minutes after thrombolytics).

Specific sources of variability fell into 4 broad categories: artifact rejection; anterior ST depression; data gaps; and operator error. Judgements on the signal vs. noise content of any particular ECG led to interpretative discrepancies only when the ST levels during that period were low. In such instances, the interpretation of "new" ST changes represented by a worrisome looking but noisy ECG might best be interpreted in the context of a real patient's clinical status rather than through a "stand-alone" ST recovery analysis. New technical strategies in noise filtration may also help with this problem. Predominant anterior ST depression, particularly in the setting of resolving inferior ST elevation, remains a dilemma, albeit a relatively infrequent one. With larger data sets we may in fact be able to improve these methods by using criteria specific to each infarct artery's location, including better discrimination between a posterior infarction and an inferior infarction with concomitant anterior ST depression. Gaps in the data stream are best treated through their elimination. More widespread use of ST-segment monitoring in chest pain evaluation and expanded memory capabilities within the devices themselves both seem likely to help avoid this problem. Operator error and fatigue may be minimized by carefully increased automation in the more quantitative and labor intensive sections of the analysis program. Effective didactic training and experience undoubtedly will also help maximize the uniform application of the method's rules and conventions.

With sufficient reliability within and across human operators, data from analyses conducted by different individuals or in different institutions may be able to provide comparable information. We conclude that the characterization of infarct artery patency, time to reperfusion, and stability of reperfusion using continuous ST-segment recovery analysis can be learned and applied with just such reliability.

ACKNOWLEDGEMENT

The authors would like to thank Ms. Ruth G. Surigao for her invaluable assistance in the preparation of this manuscript.

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Chapter 4

Evolution of an Automated ST-Segment Analysis Program for Dynamic Real-time, Noninvasive Detection of Coronary Occlusion and Reperfusion

Evolution of an Automated ST-Segment Analysis Program for Dynamic Real-time, Noninvasive Detection of Coronary Occlusion and Reperfusion

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Abstract: Patients in whom early and stable reperfusion through the infarct artery fails after thrombolytic treatment might benefit from further revascularization therapy. A reliable noninvasive technique able to detect both reperfusion and reocclusion would be useful to test this hypothesis. However, no such technique presently exists. ST-segment recovery analysis using continuous digital 12-lead ST monitoring has been shown to be an accurate predictor of infarct artery patency in real time. This method was dependent on a trained clinician's analysis of the recordings on a personal computer. For optimal bedside application, salient principles of this ST-segment recovery analysis were converted into algorithms and built into the ST monitor software. The essentials of these algorithms are described in this report. **Key words:** acute myocardial infarction, patency assessment, noninvasive, ST-segment, continuous electrocardiography, automated algorithm.

Patients in whom early and stable reperfusion through the infarct artery fails after thrombolytic treatment might benefit from further revascularization therapy.[1–9] A reliable, noninvasive assessment technique able to detect both reperfusion and reocclusion of the infarct artery would be useful to determine the need for further reperfusion therapy, and would thus enable the testing of this hypothesis. However, no reliable, practical technique has been reported. The Duke University method of ST-segment recovery analysis, using dynamically updated measurements during continuous digital 12-lead ST monitoring, has been shown in the Thrombolysis and Angioplasty in Myocardiol Infarction (TAMI) 7 trial to predict infarct artery patency in a real time emulation.[10,11] As a component of the TAMI 7 trial design, serial analysis loops of prospective patient sets were used to distill logistic principles from the original heuristic method of ST recovery analysis.[12] This method was dependent on a trained clinician using an off-line personal computer for completion of the analysis. For optimal bedside application, patency assessment based on ST-segment recovery

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analysis should be an on-line component of a bedside ST monitor. As the next step in device evolution to the level of practical utility, salient principles of the Duke method were converted into algorithms and incorporated into a portable interactive bedside ST monitor. The essentials of this automated patency assessment program are described in this report.

Materials and Methods

ST-Segment Monitor

The 12-lead ST-segment monitor has been previously described in detail.[13,14] Briefly, the ST monitor (ST100, Mortara Instrument, Milwaukee, WI) acquires and digitizes standard 12-lead electrocardiograms (ECGs) every 20 seconds, recognizing QRS onset in all 12 leads simultaneously and creating a "median beat" complex out of each 10 second acquisition period. The first acquired ECG is used as a reference for comparison of ST-segment amplitudes measured at 60 ms after J point. If subsequent ECGs show a change in ST-segment amplitude more than a preset threshold, normally 200 μV in a single lead or 100 μV in two leads, the violating ECG plus another eight ECGs are stored over a 3 minute period, after which the last recorded ECG serves as an updated reference. In the absence of ST-segment amplitude changes an ECG is stored every 20 minutes by default. Trendlines of ST-segment deviation versus time are stored for all 12 leads, using the measurements in all median beats, for later use in the patency assessment algorithm. Torso lead placement in fixed positions with radiotranslucent electrodes and impedance-regulated skin prep (Quik Prep, Quinton Medical, Seattle, WA) are used to reduce noise.

Patency Assessment Algorithm

Continuously updated surveillance of all 12 leads is used to select the most active lead, defined as the single lead showing the highest ST-segment elevation up to that moment in the monitoring period. Amplitude measurements in this most active lead are then used to identify two ECGs used for comparison to the assessment ECG: the "last transition" ECG and the "maximum" ECG. The last transition ECG is defined as the last ECG prior to the assessment ECG where the trend of ST-segment amplitude over time changes from worsening (upsloping) to improvement (downsloping) or vice versa. The maximum ECG is defined as the ECG displaying the most ST-segment elevation in the most active lead during the recording period up to the moment of patency assessment. Figure 1 is a graphic display of the definition of these ECGs in three sequential periods of an ST trend during a brief occlusion of a coronary artery in a single patient. As can be seen, with each updated patency assessment, the ECGs representing the maximum ECG and the last transition ECG may change. In this example, in the upper trend the maximum ECG and the assessment ECG are the same. Minutes later, in the middle trend, as the assessment ECG is updated, the maximum and the last transition ECG are the same. Minutes later, in the bottom trend, the updated assessment ECG, the maximum ECG, and the last transition ECG each define unique ECGs.

Analog waveforms from all three ECGs (assessment, maximum, last transition) are printed in hard copy for inspection by the clinician (Fig. 2). Using a single button push, the clinician may reject any ECG that contains unacceptable noise or conduction disturbance.

After confirmation of satisfactory noise levels, two elements of ST recovery are automatically quantified: the percent ST recovery (amplitude recovery) and the peak ST trend slope between the last transition ECG and the assessment ECG (Fig. 3). The percent ST recovery is defined as the difference in the ST amplitude in the most active lead between the maximum ECG and the assessment ECG, presented as a percentage of the absolute amplitude of the maximum ECG. The peak ST trend slope is defined as the peak μV shift in the most active lead within a floating 2 minute window that runs from the assessment ECG backward in time to the last transition ECG.

Once quantified, the percent ST recovery and the peak ST trend slope are then conveyed through a simple logic flow to produce a final interpretative statement about coronary patency. Details of this logic flow are given in Figure 4. The first branch point is whether or not the maximum ST amplitude is equal to or greater than 200 μV. If "no," a special statement is printed that the amplitudes are too low to perform a patency assessment. If "yes," the next branch point asks whether ST recovery from the maximum ECG to the assessment ECG is greater or less than 50%. The third series of branch points asks whether the peak 2 minute ST slope since the last transition ECG is upsloping ($\geq$ 50 μV/2 min), downsloping ($\leq$ −50 μV/2 min), or flat. Flow through these branch points leads to an interpretative statement of vessel patency as occluded, indeterminate, or patent. Figure 5 gives an example of an actual interpretative statement printout.

Looking again at the three periods during an evolving ST trend shown in Figure 1, the dynamic

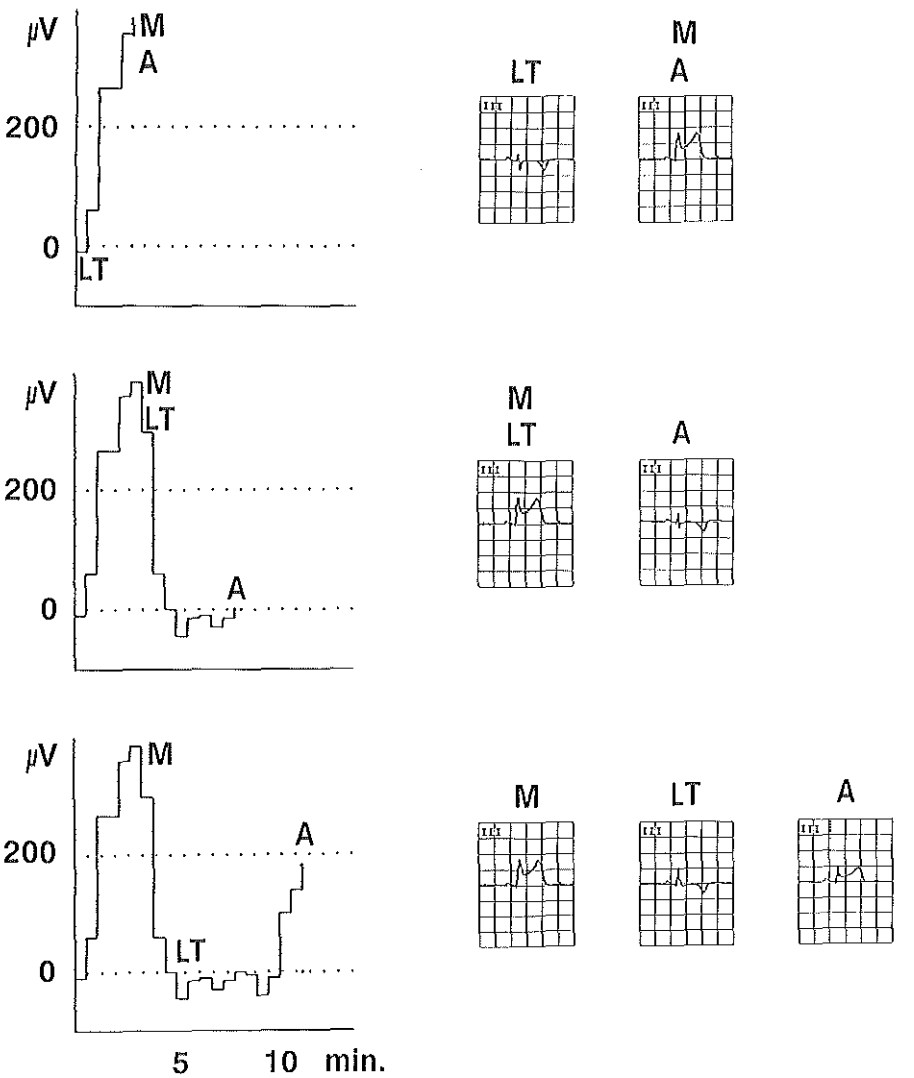

Fig. 1. Three sequential periods of an ST-trend during a brief occlusion of a coronary artery in a single patient. The positions of the three ECGs essential to the algorithm are represented by the abbreviations placed above the trend. The waveforms in the most active lead in these three ECGs are depicted on the right half. A = assessment ECG, M = maximum ECG, LT = last transition ECG.

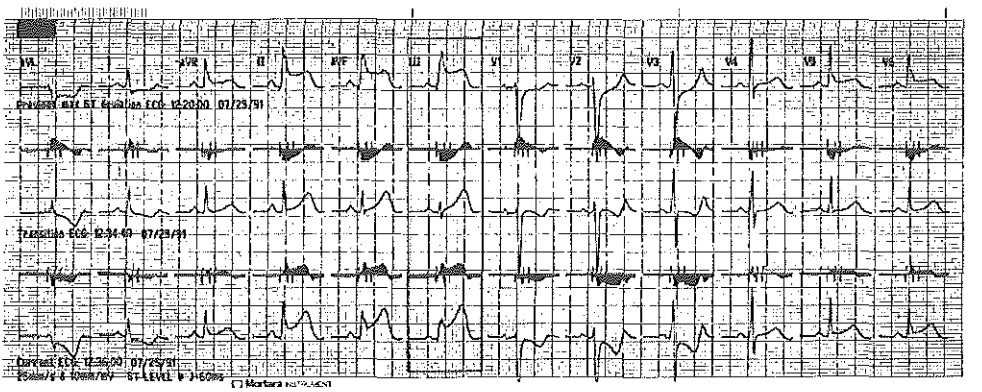

Fig. 2. ST monitor printout of the maximum ECG (top), the last transition ECG (middle), and the assessment ECG (bottom) in a comparison plot. The most active lead is captured in the rectangular box.

performance of the logic flow can be illustrated. In the upper trend, seconds after occlusion of the coronary artery, there is more than 200 μV ST elevation in the maximum ECG, the assessment ECG does not show any recovery from the maximum ECG, and the peak ST trend slope is upsloping. The program's interpretation is "occluded." In the middle trend, after reperfusion of the coronary artery, the assessment ECG shows more than 50% recovery from the maximum ECG, and the peak ST trend slope since the last transition ECG is downsloping. The program's interpretation in this case is "patent." In the bottom trend the coronary artery has reoccluded. At this time, the assessment ECG still shows more than 50% recovery from the maximum ECG; however, the peak ST trend slope since the updated last transition ECG is upsloping again. The program's interpretation at this moment is "occluded."

Discussion

The Duke University method of ST-segment recovery analysis on continuous digital 12-lead ST monitor recordings has been shown to be able to predict infarct artery patency in a real time emulation.[10,11] To make this technique practical in a critical care

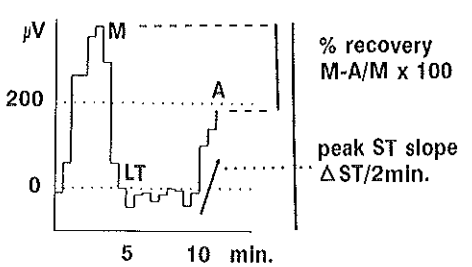

Fig. 3. Quantification of the two elements of ST-segment recovery: the recovery in ST-segment amplitude in the assessment ECG as a percentage of the maximum ECG ST-segment amplitude and the peak ST trend slope as the peak μV shift within a floating 2 minute window that runs from the assessment ECG backward in time to the last transition ECG. A = assessment ECG, M = maximum ECG, LT = last transition ECG.

Max ST ≥200μV ? —no→ no occlusion detected
↓yes

amplitude recovery	peak slope	Interpretation
< 50%	> -50μV/2min.	OCCLUDED
< 50%	≤ -50μV/2min.	INDETERMINATE
≥ 50%	≤ -50μV/2min.	PATENT
≥ 50%	> 50μV/2min.	OCCLUDED

Fig. 4. Details of the automated patency assessment program's logic flow that will lead to an interpretative statement regarding the coronary artery patency as occluded, indeterminate, or patent.

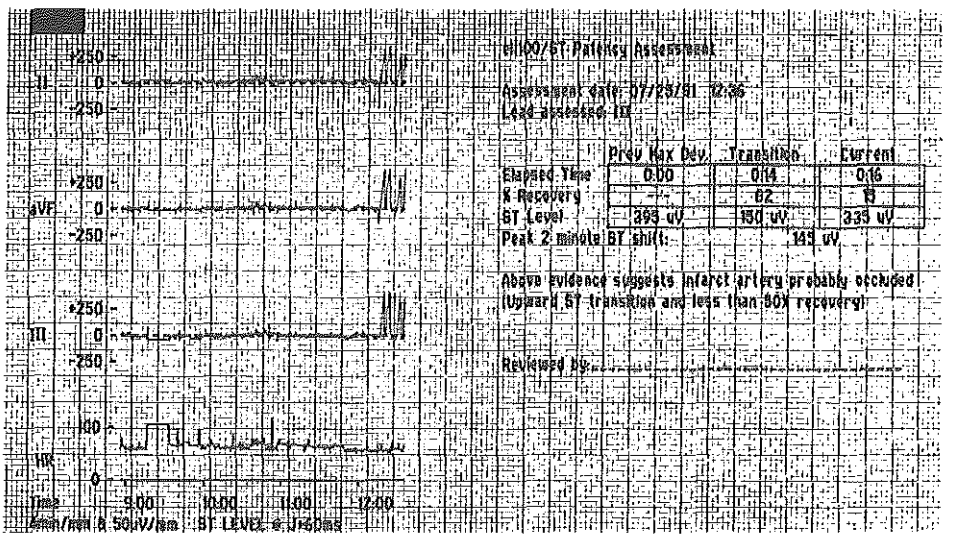

Fig. 5. Example of an ST monitor printout of the automated patency assessment. On the left half is a printout of the most active lead's trend of ST-amplitudes over time plus the trends of two consecutive leads. Measurements of ST amplitude in the maximum ECG, the last transition ECG, the assessment ECG, the percent ST recovery, and peak ST trend slope are given in the right upper corner. Under this the patency assessment is given.

setting in real time, we derived the salient principles of this method into algorithms and incorporated them into the portable bedside ST monitor itself. This report describes the essentials of these algorithms. A study to test the program's ability to detect coronary occlusion and reperfusion, using coronary angioplasty as a well-controlled human model of brief coronary occlusion and reperfusion, is currently underway. A large clinical field experience in acute myocardial infarction, including simultaneous angiographic documentation of infarct artery patency, is also underway.

The use of a minimum threshold of 200 μV ST-segment elevation in the worst lead to detect occlusion, like the use of standard 12-lead ECGs, may introduce some anatomic bias, especially with circumflex artery occlusion, which will need to be quantified. This arbitrary threshold is adopted from criteria common in many thrombolytic trials, since the intended application of the patency assessment program is in this patient group.

The simplistic nature of the program's design makes it vulnerable to artifact from noise or conduction aberrancy introducing nonischemic ST values. The clinician's ability to eliminate ECGs with these abnormalities by review of the hard copy analog waveforms at the moment of assessment provides one solution to this problem. Rather than subjecting the ECG signals to additional electronic filtering, with potential information loss, the clinician acts as the final "noise filter." Further experience with statistical filtering may obviate this need in the future.

In its current design, the program is fully operative within the portable bedside monitor on a "push-button" basis, consistent with the demands of real time use. If, with further testing, the algorithms can accurately and dynamically reassess coronary patency over time, then noninvasive monitoring for failed reperfusion or abrupt reocclusion may achieve practical capability for clinical or investigational application.

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Chapter 5

Performance of an Automated Real-Time ST-Segment Analysis Program to Detect Coronary Occlusion and Reperfusion

PERFORMANCE OF AN AUTOMATED REAL-TIME ST-SEGMENT ANALYSIS PROGRAM TO DETECT CORONARY OCCLUSION AND REPERFUSION

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ABSTRACT

Continuously updated ST-segment recovery analysis has been shown to accurately predict infarct related artery patency. Salient principles were converted into algorithms and incorporated into a portable ST monitor for optimal application. This study tested the automated program's ability to detect occlusion and reperfusion during balloon angioplasty.

All 35 inflations causing peak ST amplitudes ≥ 200 μV were detected. All five inflations causing < 200 μV were also detected, but only when preceded by an inflation causing ≥ 200 μV. Occlusion was detected a median of 40 seconds after inflation, reperfusion a median of 17 seconds after deflation. Peak ST elevation ≥ 200 μV occurred in 19/26 LAD inflations (73%), 1/22 LCX inflations (5%), and 15/30 RCA inflations (50%). Five different leads identified peak ST elevation through 12-lead surveillance.

The automated patency assessment program appears to detect coronary occlusion and reperfusion within seconds in all occlusions causing ≥ 200 μV peak ST elevation. Field testing as a practical noninvasive triage tool in myocardial infarction patients seems warranted.

INTRODUCTION

Patients suffering acute myocardial infarction in whom thrombolytic therapy fails to provide early and stable reperfusion might benefit from additional pharmacologic or mechanical revascularization therapy.[1-9] To study these patients without subjecting all patients to catheterization would require a practical, accurate noninvasive method able to detect both reperfusion and reocclusion in real time.

ST-segment recovery analysis has been shown to accurately predict infarct artery patency in a real-time emulation using dynamically updated reference measurements during continuous digital 12 lead ST-segment monitoring.[10-12] However, this method of patency assessment required transfer of the ECG data to a separate personal computer review station for further analysis by a trained clinician. To enhance bedside application, the ST-segment recovery analysis should be a component of the free standing monitor itself, accessible to less intensively trained physicians. Salient principles of the analysis method were therefore converted into algorithms and incorporated into the portable monitor as an interactive auto-

mated patency assessment program.[13] This study was designed as a first phase of testing the ability of this automated patency assessment system to detect known periods of coronary occlusion and reperfusion and the speed thereof, using angioplasty as a controlled human model.

METHODS

Population

Patients undergoing elective percutaneous transluminal coronary angioplasty of 1 or more subtotal (75-99%) stenotic lesions were selected prospectively to equally represent the three major coronary arteries. Patients with a previous coronary artery bypass operation, within the first 3 days after acute myocardial infarction, with a chronic total occlusion as a target lesion, with an abnormal conduction pattern, or undergoing an intervention with a device other than a conventional balloon, were excluded. Coronary angioplasty and ST-segment monitoring were performed according to standard practice in our institution.

ST monitoring

The 12 lead ST monitor (ST100, Mortara Instrument, Milwaukee) has been described in detail previously.[14-16] In summary, the ST monitor acquires and digitizes a standard 12 lead ECG every 20 seconds, recognizing QRS onset in all 12 leads simultaneously and creating a median beat complex out of each acquisition. For the purpose of this study, all acquired ECGs were stored in the monitor's memory. Torso lead placement[15] with radiotranslucent electrodes and impedance-regulated skin preparation (Quik Prep, Quinton Medical, Seattle) were used to reduce noise.

Automated patency assessment

Details of the automated patency assessment method have been described previously.[13] Briefly, continuously updated surveillance of all 12 leads is used to select the most active lead, defined as the single lead showing the highest ST-segment elevation up to that moment. Amplitude measurements in this most active lead are then used to identify 2 ECGs for comparison to the assessment ECG: the "last transition" ECG and the "maximum" ECG. As shown in Figure 1 the "last transition ECG" is defined as the last ECG prior to the assessment ECG where the trend of ST-segment amplitude over time changes from worsening (upsloping) to improvement (downsloping), or vice versa. The "maximum ECG" is defined as the ECG displaying the most ST-segment elevation in the most active lead during the recording episode up to the moment of assessment. With each new assessment ECG, the most active lead and the ECGs representing the maximum ECG and the last transition ECG are automatically re-defined.

Analogue waveforms from all 3 ECGs (assessment, maximum, last transition) are printed in hard copy as a comparison plot for inspection by the clinician. By pushing a button, the clinician may reject any ECG that contains unacceptable noise or conduction disturbance, after which the program selects a new ECG. After visual confirmation of satisfactory noise levels, two parameters of ST recovery are automatically calculated: 1) the ST amplitude recovery in the assessment ECG as a percentage of the maximum ECG ST amplitude; and 2) the peak 2 minute ST trend slope between the last transition ECG and the assessment ECG (Figure 1). A window between 2 points 2 minutes appart is used "floating" backward from the assessment ECG to determine the slope between these 2 points at each 20 seconds interval: wor-

sening (upsloping ≥ 50 μV / 2 minutes), improvement (downsloping ≤ - 50 μV / 2 minutes), or flat. The last transition ECG is the last ECG prior to the assessment ECG where the trend of ST amplitudes over time in the worst lead changes from upsloping to downsloping or vice versa (Figure 1).

As was previously described,[13] the results of these 2 calculations are then conveyed through a simple logic flow (Figure 2) to produce a final interpretative statement about coronary patency as "occluded", "indeterminate", or "patent". If less than 50% recovery has occurred and the peak 2 minute ST slope is flat or upsloping the infarct related artery is considered to have remained occluded. A recovery of ≥ 50% from the peak ECG as well as a peak 2 minute ST slope ≤ - 50 μV / 2 minutes is required to assess the infarct related artery as patent to differentiate from gradual amplitude diminution due to loss of myocardial mass producing injury current. If a recovery < 50% has occurred, but the peak ST slope is downsloping it is believed that this might be the advent of reperfusion without enough certainty and the patency assessment is therefore indeterminate. When 50% recovery has occurred with the required downslope of ≤ - 50 μV / 2 minutes, but is than followed by an upsloping ST trend, it is believed that this is due to recurrent occlusion of the infarct related artery and this leads to an interpretation as occluded.

If none of the recorded ECGs have an ST amplitude ≥ 200 μV, a special statement is printed that the amplitudes are below the programmed threshold to perform a patency assessment.

Endpoints

For the purpose of this study a patency assessment was performed every 20 seconds before, during and after each balloon inflation lasting at least 60 seconds. A balloon induced occlusion was considered "detected" if the program produced at least 1 interpretative statement saying "occluded" during that inflation. For all detected balloon inflations, the following performance parameters were evaluated: 1) Time from balloon inflation to the first assessment ECG with an interpretative statement saying "occluded"; 2) time from balloon deflation to the first assessment ECG with an interpretative statement no longer saying "occluded"; and 3) duration of the episode during which interpretative statements said "occluded" as compared to the actual duration of balloon inflation.

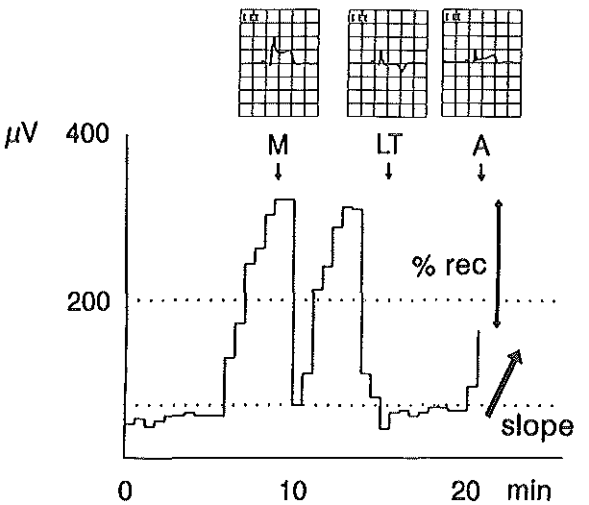
Statistics

All continuous variables are represented as median values, 25th - 75th percentile, and in relevant cases range. Categorical parameters are represented as numbers of patients or number of inflations. Detection rates are reported as absolute numbers, percentages and 95% confidence limits. Difference in detection rates over all inflations were tested using the Fisher exact test. P-values < 0.05 were considered significant.

RESULTS

A total of 78 transient coronary occlusions were recorded from 31 coronary sites in 30 patients. The recordings of 6 patients were excluded for analysis: 2 underwent PTCA of a totally occluded artery, 2 underwent angioplasty with a perfusion balloon catheter, 1 had continuous RBBB, 1 had incomplete LBBB with axis changes during inflation. Table 1 summarizes some of the characteristics of the study population. The vessel dilated was the left anterior descending artery (LAD) in 10 patients (26 inflations), the left circumflex artery (LCX)

Figure 1



ST-segment deviation over time measured in the peak lead (III) during 3 consecutive balloon inflations. The definition of the maximum ECG (M), last transition ECG (LT), and assessment ECG (A) are represented above the trendline. Two arrows on the right side represent the 2 measurements that are used in a logic flow to come to an interpretative statement regarding patency of the coronary artery: the recovery in ST elevation in the assessment ECG as a percentage of the maximum ST elevation (% rec); and the 2 minute peak slope in the trendline between the last transition ECG and the assessment ECG.

Figure 2

Max ST ≥200μV ? —no→ no occlusion detected

↓ yes

amplitude recovery	peak slope	interpretation
< 50%	flat or upsloping	OCCLUDED
< 50%	downsloping	INDETERMINATE
≥ 50%	downsloping	PATENT
≥ 50%	upsloping	OCCLUDED

Representation of the logic flow implemented in the automated patency assessment program. The 2 measurements demonstrated in Figure 1 are used to come to a final statement regarding infarct related artery patency. *Modified after veldkamp et al.: Evolution of an automated ST-segment recovery analysis program for dynamic real-time, noninvasive detection of coronary occlusion and reperfusion, J Electrocardiol. 1993 (13). With permission of Churchill Livingstone Publishing Company, New York.*

Table 1: Patient descriptors

Gender:	
male	15/30 (50%)
female	15/30 (50%)
Age:	median 68 years (quartile range 51-75, range 40-84)
Hypertension:	18/30 (60%)
Diabetes Mellitus:	12/30 (40%)
Previous AMI same region:	
non q-wave	5/30 (17%)
q-wave	5/30 (17%)
Indication:	
angina pectoris	15/30 (50%)
unstable angina	10/30 (33%)
post AMI	4/30 (13%)
syncope	1/30 (3%)
Extent of disease:	
1 vessel	14/30 (47%)
2 vessels	8/30 (27%)
3 vessels	8/30 (27%)
pre-angioplasty stenosis:	median 95% (quartile range 75-95, range 75-99)

Descriptive characteristics of the population studied. AMI = acute myocardial infarction; post AMI = > 3 days post acute myocardial infarction.

in 10 patients (22 inflations), and the right coronary artery (RCA) in 11 patients (30 inflations). Median duration of inflation was 183 seconds (quartile range 126 to 189; range 62 to 912). Median peak ST deviation per inflation was 165 μV (quartile range 34 to 258, range -190 to 968). Median peak ST deviation was 240 μV for LAD inflations (quartile range 115 to 303, range 65 to 968), - 20 μV for LCX inflations (quartile range - 95 to 15, range - 190 to 820), and 205 μV for RCA inflations (quartile range 78 to 275, range - 20 to 395). Median peak ST deviation was 175 μV for first balloon inflations (quartile range 15 to 235, range - 115 to 687) and 160 μV for repeated balloon inflations (quartile range 50 to 260, range - 190 to 968). Out of the 78 inflations, there were 35 (45%) causing ≥ 200 μV peak ST amplitude, including 19 out of 26 LAD inflations (73%), 1 out of 22 LCX inflations (5%), and 15 out of 30 RCA inflations (50%). All 35 inflations (100%) with ≥ 200 μV peak ST amplitude were detected. Of the 43 balloon inflations that caused < 200 μV ST elevation, 5 were also detected (1 LAD, 1 LCX, 3 RCA). In all 5 instances the inflation followed a prior inflation that did cause ≥ 200 μV ST elevation.

In the 40 detected inflations, median time from balloon inflation to detection of occlusion was 40 seconds (quartile range 20 to 80; range 0 to 120). Reperfusion by balloon deflation in those same 40 occlusions was detected at a median of 17 seconds (quartile range - 2 to 16, range - 92 to 126). The median duration of occlusion defined by the automated patency assessment program was 120 seconds, out of the actual median balloon inflation duration

of 181 seconds in these 40 detected inflations. During 6 inflations 1 or more ECGs were not analyzed due to conduction changes (1,2,2,3,3, and 4 consecutive ECGs excluded respectively) and 1 ECG during 1 inflation was not analyzed due to the high noise content.

After splitting the 78 balloon inflations around the median duration of inflation, no correlation was found between inflation duration and the program's detection performance ($p = 1.0$). Neither was there any difference in detection of first versus repeated balloon inflations: 15 out of 30 versus 25 out of 48 respectively ($p = 1.0$).

The precordial location of the peak lead activity varied with the artery occluded. Of the standard 12 leads monitored, the following peak leads were used to detect occlusions: leads V1 (2), V2 (8), V3 (8), V4 (2) for LAD occlusions; lead III (2) for LCX occlusions; and lead III (18) for RCA occlusions. Thus, detection of the occlusions occurred in 5 different leads.

DISCUSSION

The results of this study show that this automated patency assessment program wholly contained within the ST monitor's architecture detected all occlusions producing injury current ≥ 200 μV, equivalent to entry criteria used in some thrombolytic trials. Detection of multiple episodes of occlusion and reperfusion was within seconds of their actual occurrence. Longer inflations did not increase the chance of detection in this model. This is probably due to our standard angioplasty practice of deflating the balloon earlier if ischemia induced by the occlusion is more severe, while dilating for longer periods if the patient tolerates it well with no ischemia. In spontaneous occlusion and infarction, longer acute occlusions would be expected to produce higher ST-segment amplitudes. Repeated inflations were detected as well as first inflations. Although one might expect lower amplitudes in repeated balloon inflations, this was not the case in this population. Furthermore, after an initial occlusion causing ≥ 200 μV ST elevation the program relies on ST-trend slopes and amplitudes relative to the peak ST elevation rather than on absolute amplitudes.

It is notable that the peak lead selected varied over the precordium with the artery occluded. This suggests that automated detection of coronary occlusion is not only a matter of updated assessments of ST amplitudes, but is also dependent on the ability to select a monitoring lead central to the geographic pattern of ST deviation.[17-21]

Limitations

Elective coronary angioplasty is an imperfect model to test a program designed for acute myocardial infarction applications, as is evidenced by the fact that only 40 of the 78 balloon inflations produced enough injury current to fulfill the preset requirement of 200 μV. Taken from the entry criteria used for some thrombolytic trials, such ST levels are somewhat more common in the milieu of prolonged occlusion necrosis typical to actual acute myocardial infarction. In a standard 12-lead ECG format, such criteria have been demonstrated to promote an anatomic bias against left circumflex artery occlusions[17] and is unfortunately paralleled in these data taken during coronary angioplasty with markedly lower peak amplitudes during occlusions of the left circumflex artery. In this regard the PTCA model emulated acute myocardial infarctions well, with most left circumflex balloon occlusions failing to produce the minimum injury current required by the automated patency program.

Despite these limitations coronary angi-

oplasty provides a human model of coronary occlusion and reperfusion of known duration and location, which is very usefull for preliminary testing of a prototype patency assessment program. Every recorded ECG could thus be correlated with simultaneous angiographic documentation of the location and flow status of the artery. The previous work on which this program was modelled has demonstrated that during infarction the myocardium generates and resolves injury current abruptly enough to make continuous ST recovery analysis a usefully accurate non-invasive marker of patency.[10-12] The results in this study suggest that further investigation into the performance of the auto-mated patency assessment program during actual acute myocardial infarction is warranted.

The time course of ST-segment change during acute myocardial infarction may be substantially different from trends obtained during coronary angioplasty and might be more heterogenous. Whether the anatomic bias or the overall performance of the program could be further optimized by changing minimal amplitude requirements or slope rates is beyond the scope of this balloon angioplasty model and needs further investigation in the acute myocardial infarction setting. Use of additional leads or modified lead systems might also enhance performance,[20, 21] especcially to reduce the anatomic bias against left circumflex artery occlusions, although the 12-lead system is practical due to universal familiarity. The variety of leads used to detect coronary occlusion suggest that more restricted lead systems would risk decreasing the accuracy of the algorithm. It would also diminish the ability to compare the precordial multilead "fingerprint" patterns that are useful in discriminating reocclusion of the culprit lesion from other sources of ST-segment deviation.[17-20] Other modifications to reduce the anatomic bias and increase the program's sensitivity, such as variable thresholds, use of reciprocal ST depression, or coronary artery specific algorithms may also bear exploration.

Clinical implications

Within the controlled setting of coronary angioplasty the automated patency assessment program appears to be capable of noninvasive detection of coronary occlusion and reperfusion within seconds of their occurrence. Contained entirely within the architecture of a portable bedside ST monitor, this automated patency assessment program might become a practical and valuable tool in the management of acute myocardial infarction patients following thrombolytic therapy. A large clinical field experience, testing the program during actual acute myocardial infarction is currently ongoing in a multicenter trial.

ACKNOWLEDGEMENTS

The authors are greatly indebted to A. Karen Loeffler and Suzanne E. Crater for their effort in gathering the data. We thank the staff and personnel of the Interventional Coronary Catheterization laboratory for their help in this project. We also thank Galen S. Wagner for carefully and critically reviewing the manuscript.

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Chapter 6

ST-Segment Deviation on the 12-Lead Electrocardiogram During Acute Myocardial Infarction: Optimal Leads for Continuous ST-Segment Monitoring

ST-SEGMENT DEVIATION ON THE 12-LEAD ELECTROCARDIOGRAM DURING ACUTE MYOCARDIAL INFARCTION: OPTIMAL LEADS FOR CONTINUOUS ST-SEGMENT MONITORING

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ABSTRACT

Continuous ST-segment recovery analysis has been proven to be a useful non-invasive indicator of failed reperfusion or recurrent occlusion of the infarct related artery. Lead systems other than those proposed for arrhythmia detection might proof superior for this purpose. Electrocardiograms recorded in 361 Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 9 trial patients were analyzed and related to the angiographically determined infarct related artery. The right coronary artery was the infarct related artery in 179 patients (50%). Lead III was most elevated in 156 (87%) and injury current was predominantly located in lead III, aVF, and II. The left anterior descending artery was the infarct related artery in 142 patients (39%). Most elevated were leads V2-V4 in 139 (98%) and those were also most often involved in the injury current pattern. The left circumflex artery was the infarct related artery in 39 patients (11%). Location of their most elevated lead was more dispersed: 17 (44%) in III, 7 (18%) lead II, 5 (13%) lead V5, and 4 (10%) lead V6 as was the injury current pattern. 330 Patients (91%) had ≥ 1 lead with ≥ 200 μV ST elevation. Combining leads III, V2, and V5 would record at least 1 lead with ≥ 200 μV ST elevation in 321 patients (89%).

CONCLUSION: *For continuous ST-segment recovery analysis a 3 lead system should be adequate to record at least 1 lead with sufficient ST deviation in a majority of myocardial infarction patients selected for thrombolytic therapy. Twelve-lead or vectorcardiographic ST-monitoring systems will increase the sensitivity for ST deviation especially in smaller infarctions and will facilitate comparison of the ST deviation pattern during recurrent elevation with the primary ST elevation episode to assess whether it indeed signifies reocclusion.*

INTRODUCTION

Continuous ST-segment recovery analysis has been shown to be a useful noninvasive indicator of failed reperfusion or recurrent occlusion of the infarct related artery. The presence of rapid ST recovery coincides with reperfusion of the infarct related artery, while rapid ST re-elevation in the same precordial pattern as the primary pattern indicates reocclusion at the same coronary location.[1-4] With this technique

different therapeutical strategies to achieve early and stable reperfusion can be compared.[5-7] Implementation in coronary care monitoring systems can lead to a better selection of patients who have received intravenous thrombolytic therapy for additional treatment such as rescue angioplasty or a regimen "tailored" to their own reperfusion behavior.[8-10] So far electrocardiographic lead systems for monitoring have been oriented to arrhythmia detection in acute coronary care or ambulatory studies and various modifications have been proposed for arrhythmia analysis or ischemia monitoring during exercise electrocardiography or using Holter monitoring systems.[11-14] Other lead sets might proof superior for the purpose of ST-segment monitoring during acute myocardial infarction.

The purposes of this study are to determine the optimal lead positions and number of leads for continuous ST-segment monitoring of patients with acute myocardial infarction in correlation with the angiographically determined infarct related artery.

METHODS

Patient population

All 430 patients from the multicenter Thrombolysis and Angio-plasty in Myocardial Infarction (TAMI) 9 trial were considered for this study. Details and main outcomes of this study have been published previously.[15] Briefly, patients presenting within 6 hours after symptom onset, without contra-indications for thrombolytic therapy, and able to give informed consent were eligible. Enrollment in the TAMI 9 trial required ST elevation ≥ 100 μV measured 0.02 seconds after J-point in ≥ 2 of the precordial leads or in ≥ 2 inferior leads with ST depression ≥ 100 μV in the anterior leads. Patients were randomized to standard treatment with "front-loaded" recombinant tissue plasminogen activator or to additional treatment with Fluosol^{lm}, a perfluorocarbon with oxygen carrying capacity.

Excluded for the purpose of this study were 35 patients in whom no coronary angiography was performed, 4 patients with an indeterminable infarct related artery, 13 patients with right or left bundle branch block, and 17 patients without any recorded electrocardiogram prior to treatment or during the acute phase of myocardial infarction. Therefore the remaining population consisted of 361 patients or 84% of the total TAMI 9 population. In the study population 73% of the patients were male, 43% had multi-vessel or left main disease, and the median age was 58 years, ranging from 22 to 88 years. Median time from onset of symptoms to onset of thrombolytic therapy was 153 minutes, with a quartile range of 107 to 215 minutes, and a range of 30 to 525 minutes.

Electrocardiographic analysis

Together with other information a copy of the enrollment electrocardiogram had to be transmitted to the central databank and coordination center. Per protocol ST-segment moni-toring with the Mortara ST 100 continuous digital 12 lead electrocardiograph was initiated prior to or as soon as possible after onset of thrombolytic therapy and continued for 24 hours. The essentials of this automated device and it's applications have been described previously.[16, 17] All electrocardiograms recorded with the ST monitor were transferred to a floppy disk for later analysis in the core laboratory with a personal computer based program (3D, Tampa Cardiovascular Associates, Tampa, Florida). As described previous-ly,[1,16] this program allows analysis of the ST monitor recording 12 lead electrocardiograms in full disclosure as well as in a 3 dimensional trend of ST

deviation over time in each lead. For the purpose of this study the maximally deviated single lead defined by the maximum ST elevation or reciprocal ST depression representing transmural ischemia in either the enroll-ment electrocardiogram or the ST monitor recording was determined for each patient, measuring the ST-segment 60 milliseconds after the J-point. If more than one lead displayed maximal ST deviation, the one with the most ST deviated contiguous lead was selected as the maximum lead. In the electrocardiogram displaying maximum deviation the deviation in the other leads was annotated for further analysis.

Angiography

A protocol coronary angio-graphy was scheduled pre-discharge, on clinical demand an emergency catheterization could be performed as well.[15] Cine-angiograms were then analyzed at the core angiographic laboratory at the University of Michigan. Criteria for the selection of the infarct related artery were: 1) the presence of occluding or severely stenosing lesions; 2) Thrombolysis In Myocardial Infarction (TIMI) flow grade; 3) presence of thrombus, haziness, or filling defects; and 4) wall motion defects. At least 2 different observers determined the infarct related artery, in case of disagreement a consensus was sought. In some unclear cases the enrollment electrocardiogram was also used to correlate with the angio-graphic information. Depending on these findings patients were divided into 4 infarct related artery groups: 1) the Right Coronary Artery (RCA) including the posterior descending branch; 2) the Left Anterior Descending (LAD) including diagonal branches and the ramus intermedius; 3) the Left Circumflex (LCX) including marginal branches and posterolateral branch; and 4) The Left Main Stem (LM).

Data analysis

Taken over all patients as well as per infarct related artery location the most elevated or peak lead was determined. The presence of ST depression as reciprocal injury current from the posterior left ventricular wall was also analyzed when this ST depression had higher absolute amplitudes than the ST elevation present in any of the elevated leads. The frequency of occurrence of ST-elevation $\geq$ 200 μV in each lead for all patients and separated per infarct related artery was also analyzed. Median, 25th and 75th percentiles of ST deviation in each lead for the patients with RCA, LAD, or LCX occlusion were determined. Optimal combinations of 1, 2, ...12 leads were sought to include as many patients as possible with at least one lead with $\geq$ 200 μV ST eleva-tion in the combination of leads.

RESULTS

From the 361 patients selected for this study 179 (50%) had the Right Coronary Artery (RCA) as the infarct related artery, 142 (39%) the Left Anterior Descending (LAD), 39 (11%) the Left Circumflex (LCX), and 1 the left main stem. The electrocardiogram selected as peak electrocardiogram for further analysis was the enrollment electrocardiogram in 200 patients (55%), in the remaining 161 patients the peak electrocardiogram selected was recorded with the digital ST recorder. The median time from the peak electrocardiogram to thrombolytic treatment was 18 minutes, with the peak ECG ranging from 267 minutes before treatment (treatment delay) to 786 minutes thereafter (late peak ECG). In a total of 228 patients (58%) the electrocardiogram selected was recorded prior to thrombolytic treatment and in 133 thereafter.

For the 179 patients with the RCA as an

Table 1: Listed are 16 patients in whom ST depression amplitude considered to represent reciprocal injury current exceeded the maximum ST elevation amplitude present. Shown for each patient is the location of the most elevated (ST↑) and the most depressed lead (ST↓) and their amplitudes.

#	IRA	ST↑	amplitude (μV)	ST↓	amplitude (μV)
1	RCA	III	150	V2	- 200
2	RCA	III	250	V2	- 300
3	RCA	III	150	V3	- 250
4	RCA	III	230	V3	- 250
5	RCA	III	494	V3	- 504
6	RCA	III	200	V3	- 500
7	RCA	III	400	V3	- 500
8	RCA	II	200	V2	- 300
9	LAD	aVL	297	III	- 430
10	LCX	III	85	V4	- 518
11	LCX	III	100	I	- 150
12	LCX	III	500	V2	- 550
13	LCX	III	460	V3	- 670
14	LCX	II	100	V3	- 150
15	LCX	II	400	V2	- 500
16	LCX	V5	295	V3	- 415

infarct related artery lead III was the most elevated lead in 156 (87%). For the 142 patients with the LAD as an infarct related artery one of the leads V2-V4 were the most elevated lead in 139 (98%). The most elevated leads for the 39 patients with an LCX as the infarct related artery were more widely dispersed: 17 (44%) with lead III, 7 (18%) with lead II, 5 (13%) with lead V5, and 4 (10%) with V6. The 16 patients (4% of the study population) in whom the peak electrocardiogram showed more ST deviation in the depressed leads than in the elevated leads are listed in Table 1. In 14 of these patients the electrocardiogram suggested infarction of the posterior wall. The maximum ST deviation in those patients was most often seen in leads V2 or V3.

Table 2 shows the frequency of occurrence of ST-elevation ≥ 200 μV in each lead for all patients and separated per infarct related artery. The distribution of leads with ≥ 200 μV of injury current followed a similar pattern as the distribution of the peak leads per infarct related artery. The inferior lead III and to a lesser extent II and aVF were most often involved in the pattern of injury current in patients with the RCA as their infarct related artery. The anterior leads V2-V4 were most often involved in the patients with the LAD as their infarct related artery. For the patients with the LCX as the infarct related artery the pattern of injury involved inferior, anterior as well as apical leads.

Figure 1 shows the median, 25th and 75th percentile of ST deviation in each lead for the three infarct related artery groups. For the patients with the RCA as infarct related artery the highest amplitudes were seen in lead III. For the patients with an

Table 2: Occurrence of ST-elevation ≥ 200 μV in each lead for all patients and separated per infarct related artery.

	RCA (n=179)	LAD (n=142)	LCX (n=39)	All (n=361)
aVL		14 (10%)	1 (3%)	15 (4%)
I		47 (33%)		10 (3%)
-aVR	26 (15%)	4 (3%)	5 (13%)	35 (10%)
II	126 (70%)	3 (3%)	21 (53%)	150 (42%)
aVF	138 (77%)	2 (1%)	22 (55%)	162 (45%)
III	155 (87%)	3 (3%)	21 (54%)	179 (50%)
V1	12 (7%)	60 (42%)	1 (3%)	73 (20%)
V2	4 (4%)	126 (89%)	5 (13%)	137 (38%)
V3	21 (12%)	123 (87%)	3 (8%)	148 (41%)
V4	27 (15%)	114 (80%)	6 (15%)	147 (41%)
V5	37 (21%)	63 (44%)	11 (28%)	111 (31%)
V6	34 (19%)	18 (13%)	15 (38%)	67 (19%)

LAD as the infarct related artery the highest amplitudes were seen in lead V3 with lead V2 as a close second. For the patients with the LCX as the infarct related artery the highest amplitudes were seen in the inferior leads II, aVF, III.

Optimal combinations of 1, 2, ...12 leads were sought to include as many patients as possible with at least one lead with ≥ 200 μV ST elevation in the combination of leads. The maximum percentage of patients achievable with combinations of 1, 2, ... 12 leads are shown in Figure 2. Of the 361 patients included 330 or 91% had at least 1 lead out of the 12 leads with ≥ 200 μV ST elevation. All of these 330 patients would have at least 1 lead with ≥ 200 μV ST elevation in a combination of 8 leads, excluding - aVR, aVF, V1, and I. Suboptimal results were achieved with combinations of 2 or 3 leads, being 310 or 86% of the patients with the combination of leads III and V2 and 321 or 89% of the patients with the combination of leads III, V2, and V5. Table 3 lists the most optimal combinations of 2 or 3 leads to have as many patients as possible with at least 1 lead with ≥ 200 μV ST elevation within the combination of leads.

DISCUSSION

In this study optimal lead sets were sought for the purpose of continuous ST-segment monitoring either as a bedside (CCU) monitoring system or for ischemia monitoring in comparative trials. Peak electrocardiograms of 361 myocardial infarction patients enrolled in the TAMI 9 trial, all with protocol coronary angiography and ST-segment monitoring for 24 hours, were therefore analyzed and compared with the angiographically determined infarct related artery. Most elevated leads and distribution of ST elevation over the 12 leads monitored were markedly different for patients with an LAD occlusion versus those with an RCA or LCX occlusion. The latter 2 groups are indistinguishable on the standard 12 lead electrocardiogram as has been published previously.[18] Monitoring of reciprocal ST depression as a reflection of posterior injury current might be useful in a small subset of patients in whom the

Table 3: Optimal combinations of 2 and 3 leads respectively to detect at least one lead with ≥ 200 μV ST elevation in as many patients as possible. The listing of combinations ends where the 95% confidence interval (between brackets) from a combination falls outside the 95% confidence interval of the combination listed as best.

2 leads			3 leads		
III, V2	86%	(82-89%)	III, V2, V5	89%	(86-92%)
III, V3	84%	(81-88%)	III, V2, V4	89%	(86-92%)
III, V4	82%	(78-86%)	III, V2, V3	88%	(85-91%)
aVF, V2	81%	(77-85%)	III, V2, V6	87%	(84-91%)
aVF, V3	80%	(76-84%)	III, V3, V5	87%	(84-90%)
II, V2	78%	(74-82%)	II, III, V2	87%	(84-90%)
aVF, V4	77%	(73-81%)	III, V3, V4	86%	(83-90%)
....			III, aVF, V2	86%	(83-90%)
			III, V1, V3	86%	(83-90%)
			III, aVL, V2	86%	(83-90%)
			III, V3, V6	86%	(82-89%)
			III, V1, V2	86%	(82-89%)
			III, -aVR, V2	86%	(82-89%)
			I, III, V2	86%	(82-89%)
			II, III, V3	86%	(82-89%)
			III, aVL, V3	85%	(81-89%)
			III, aVF, V3	85%	(81-89%)
			III, V1, V4	84%	(81-88%)
			III, -aVR, V3	84%	(81-88%)
			I, III, V3	84%	(81-88%)
			aVF, V2, V4	84%	(80-88%)
			aVF, V2, V3	84%	(80-88%)
			aVF, V2, V5	84%	(80-88%)
			aVF, V2, V6	83%	(79-87%)
			III, aVL, V4	83%	(79-86%)
			III, V4, V6	83%	(79-86%)
			III, V4, V5	83%	(79-86%)
			aVF, V3, V5	82%	(78-86%)
			II, III, V4	82%	(78-86%)
			aVF, V3, V4	82%	(78-86%)
			aVF, V1, V3	82%	(78-86%)
			III, aVF, V4	82%	(78-86%)
			II, aVF, V2	82%	(78-86%)
			...		

Figure 1: Median (squares) and quartile ranges (bars) of amplitudes in the 12 leads separated per infarct related artery.

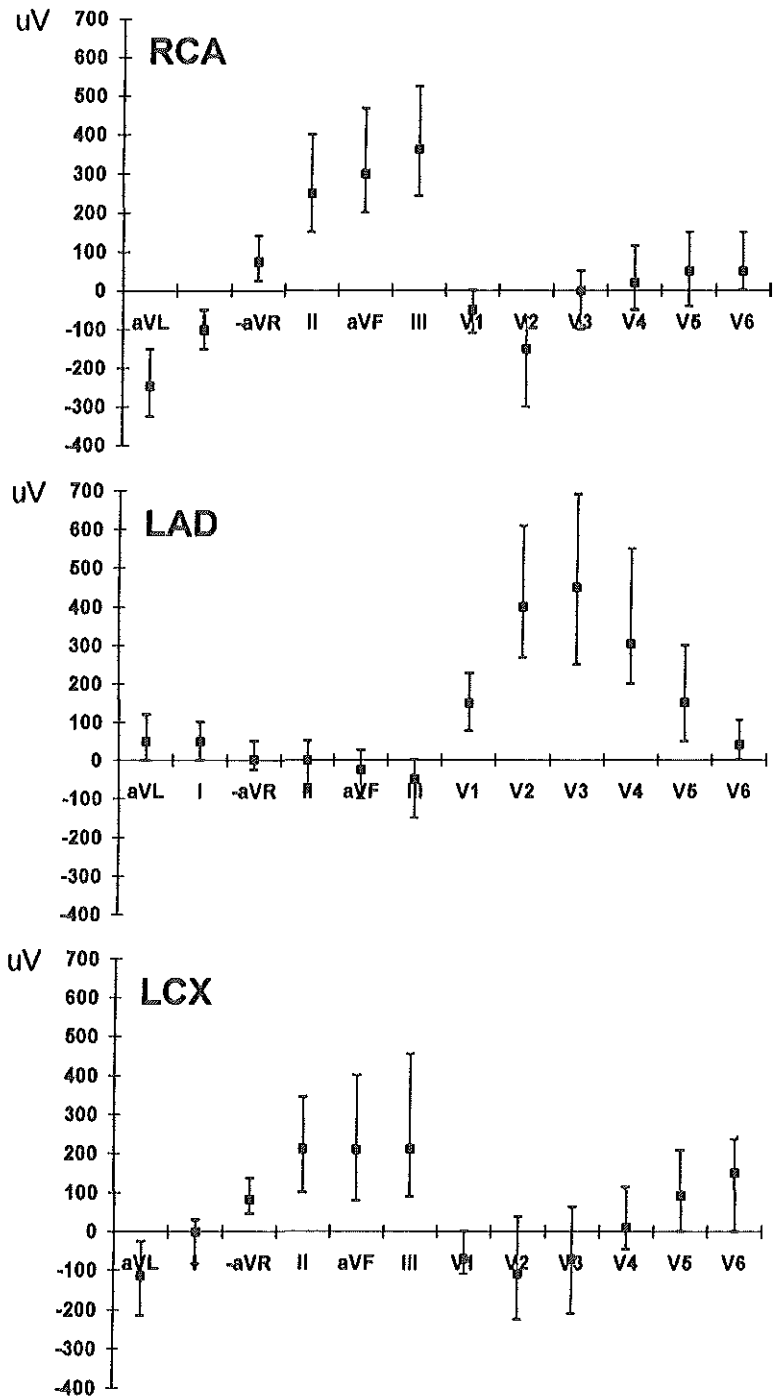
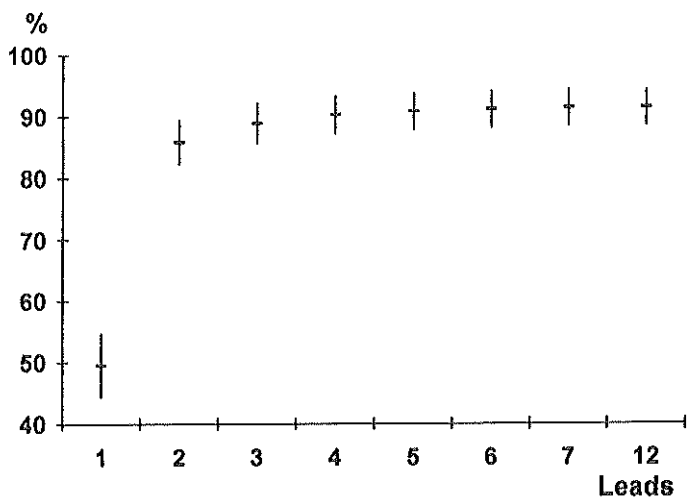


Figure 2: Sensitivity of detecting occurrence of at least 1 lead with ST-elevation ≥ 200 μV in the most optimal combination of 1 to 12 leads respectively. Most optimal combinations were: 1. III; 2. III + V2; 3. III + V2 + V5; 4. III + V2 + V3 + V5; 5. III + V2 + V3 + V5 + V6; 6. III + V2 - V6; 7. III + aVL + V2 - V6; 8. III + aVL + V1 -V6; 9-12. at random plus I, II, aVF, -aVR. Vertical bars indicate the 95% confidence intervals.



reciprocal change has markedly more ST deflection than the ST elevation commonly seen in the inferior or apical leads. This reciprocal ST depression is normally maximal in lead V2 or V3. From the data derived in this study combinations of monitoring leads can be proposed. It seems logical to distinguish the options according to technical possibilities of lead systems.

1-lead system

A single lead system seems archaic now most CCU monitoring sys-tems and Holter recorders offer at least 2 monitoring leads. However, the option of dedicating one lead to arrhythmia moni-toring (e.g. an "atrial lead") while the other lead is dedicated to ST-segment monitoring must be considered. Clearly, no fixed lead position can be recommended since anterior infarctions have such dif-ferent injury current patterns than inferior, lateral, or posterior infarctions. To suit the variety of ST elevation patterns, an ex-ploring lead would be necessary. The placement of this lead should be guided by for instance the 12-lead electrocardiogram, looking for the maximum injury current detectable. This requires skillful interpretation of the electrocardiogram by trained personnel and is probably prone to error in emergency situations.

2- and 3-lead systems

These are the lead systems commonly seen in CCU moni-toring systems and Holter recorders. An optimal 2 lead system would have 1 lead oriented inferiorly (III or aVF) and one anteriorly (V2 or V3). The inferior lead would detect the injury current in patients with an RCA occlusion as well as many of the patients with an LCX occlusion. The anterior lead would detect the injury current in patients with an LAD occlusion as well as the reciprocal ST depression in patients with a posterior infarction (RCA or LCX occlusions). In a 3-lead

system an apically oriented lead should be added (V5). This lead would add sensitivity for ST elevation especially in patients with an LCX occlusion. A combination of 2 and 3 leads was able to detect an injury current of ≥ 200 μV in 310 and 321 out of 330 patients with at least 1 lead exceeding 200 μV respectively. However, this would not necessarily be the peak lead. The combination of leads III and V2 would capture the peak lead in only 238 or 66% of the patients and this would be so in 248 or 69% for the combination of leads III, V2, and V5. If patency prediction algorithms are used based on absolute amplitudes a lead system containing more than 3 leads should be preferred.[2] It has been shown that accuracy of continuously updated ST-segment recovery analysis is related to the maximum recorded ST amplitude.[19, 20] It may be speculated that a patency algorithm based on relative recovery of ST elevation and or ST-recovery and re-elevation slope rates may be less dependent on the maximum recorded ST amplitude, but this remains to be tested.[21] Furthermore, a Holter recorder lead set with orthogonal orientations can be used with the possibility of reconstructing a full 12-lead electrocardiogram. This option will be discussed later.

Multi-lead systems

As shown in Figure 2 little sensitivity for detecting injury current is added when combinations of more than 3 leads are used. As mentioned before however, the chance of finding a lead with higher ST elevation does increase markedly when more leads are added. A logic lead system would be the 12-lead system due to its universal familiarity. The data for this study where derived from continuous electrocardiogram recordings made with a continuous digital 12 lead ST-segment monitor that is commercially available (ST100, Mortara Instrument, Milwaukee). As described previously,[1, 2, 13, 22] the use of multiple leads enhances the possibility to recognize reocclusions as a "fingerprint" of the first recorded occlusion. Reocclusion of the same coronary artery gives a matching fingerprint of ST deviation over the precordium, although absolute amplitudes might be different. If ST deviation occurs in a different pattern, either as depression alone or as elevation in a different lead pattern, thus not matching the fingerprint, there is an increased chance that this is not due to a reocclusion of the infarct related artery. The use of multiple leads will optimize the chance of recording the maximum ST-segment amplitude, thereby leading to better recognition of the dynamic ST changes and improved accuracy of continuously updated ST-segment recovery analysis.[19, 20] Use of additional leads or modified lead systems might also enhance continuous ST-segment monitoring, especially in isolated high lateral or posterior infarction, but clinical experience with these lead systems is limited.[23, 24]

Orthogonal leads

An orthogonal lead system, such as proposed by Frank [25] deserves attention since it is used in a commercially available ST-monitoring unit as well.[3, 26] Strictly spoken it is a 3 lead system with lead orientations directed inferiorly, anteriorly, and laterally. Parameters derived from the vector loops and their development over time however are independent of these orientations. In addition one can reconstruct a 12 lead electrocardiogram through the so called Dower transformation.[27] One can also reconstruct the maximum single ST vector at a fixed time after the J-point, thereby reconstructing a "virtual exploring lead" towards the epicenter of the current of injury. Although on theoretical grounds one might expect greater sensitivity for ST

deviation with this lead system, the advantage relative to the standard 12-lead system has not been proven in clinical applications. Furthermore, the exactness of the Dower transformation derived leads relative to a true lead registration should be investigated in abnormal electrocardiograms.

Limitations

The entry criteria for the TAMI 9 study required minimal ST elevation present in 2 precordial leads or in 2 inferior leads with ST depression in the anterior leads. This has introduced a bias against small infarctions, especially of isolated high lateral and posterior location. Thereby this study can not answer whether the proposed lead sets are suitable to these infarct locations as well. However, the proposed anterior leads V2 or V3 can be expected to be able to detect posterior injury current as reciprocal change if enough current is generated. The advantage of taking a trial population for this study on the other hand is that all patients received protocol angiography and continuous ST-segment monitoring so that data are less biased by clinical presentation.

The choice of 200 μV as a threshold for selecting optimal lead combinations seems rather arbitrary. At this level of ST deviation changes due to reperfusion or reocclusion of the infarct related artery can be clearly distinguished from random noise. In the setting of coronary angioplasty we have shown that an algorithm based on relative recovery and slopes of ST recovery over time rather than absolute changes is able to detect reperfusion and reocclusion with high accuracy, independent of the maximum amplitude present in the lead observed.[28]

Clinical implications

For continuous ST-segment monitoring a 3 lead system should be adequate to record at least 1 lead with sufficient ST deviation in a majority of patients selected for thrombolytic therapy. Previously Aldrich proposed a 2 lead system consisting of III and V2.[11] Krucoff et all. proposed a 3 lead Holter system with inferior (aVF), anterior (V2), and inferolateral orientation (V5).[13] The study by Alldrich interpreted ECGs with an anterior pattern (n = 68) or an inferior pattern (n = 80) without correlation with infarct related arteries determined through coronary angiography. The lead set proposed by Krucoff et all. was not based on patient data. A task force of the American Heart Association came with specific recommendations for electrocardiographic monitoring in special care units.[29] Based on the studies by Alldrich and by Krucoff they suggested the use of 3 pseudo-orthogonal leads, one oriented anteriorly (V1 or V2), one inferiorly (aVF), and one apically (V5). This combination is expected to give sufficient information for rhythm analysis and ST-segment monitoring. These data confirm their proposed 2 and 3 lead systems respectively in an independent larger group of patients who underwent protocol coronary angiography for the purpose of continuous real-time ST-segment monitoring. Hohnloser et all. published a study using a 2-channel Holter recorder with leads oriented towards V5 and aVF to assess the patency assessment accuracy of ST-segment recovery analysis.[30] Only 65% of the patients exhibited ≥ 1 mm ST elevation in at least 1 lead, thus in 35% of the patients the recording failed to display sufficient amplitudes for further analysis.

More important is the finding that a limited set of preferably 3 leads can be applied for the purpose of continuous ST-segment monitoring without a profound loss in sensitivity for ST deviation as compared to multiple lead systems. Whether

accuracy of continuously updated ST-segment recovery analysis is affected by the decreased maximum ST amplitude recorded remains to be tested.[19, 20] The possibility of lead reduction has been shown previously under the different physiologic circumstances of exercise electrocardiography.[14] In that study a (pseudo) orthogonal lead system was proposed, similar to the lead set proposed in our data.

The importance of matching the re-elevation pattern ("fingerprinting") to the original pattern of ST deviation would require in these systems that for instance a standard 12-lead electrocardiogram is recorded whenever there is suspicion of recurrent ST elevation. A full 12-lead ST monitoring system or an ST monitoring system based on orthogonal leads could facilitate these procedures and increase sensitivity for ST elevation in smaller infarcts, especially in high lateral locations. The possibility of alternate leads or lead systems outside the conventional 12 lead system should be explored for the purpose of continuous ST-segment monitoring.

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Chapter 7

ST-Segment Recovery Endpoints in Clinical Trials: Past, Present, Future

ST-Segment Recovery as an Endpoint in Acute Myocardial Infarction Trials

Past, Present, and Future

Rolf F. Veldkamp, MD, James E. Pope, MD, Sharon T. Sawchak, RN, Galen S. Wagner, MD, Robert M. Califf, MD, and Mitchell W. Krucoff, MD

Abstract: Traditional, comparative acute myocardial infarction trials have used morbidity and mortality as endpoints, requiring large study populations. Left ventricular function and angiographic infarct-related artery patency have, therefore, been used as alternative endpoints. These assessments are costly, risk-laden, and put a large demand on resources not available in every hospital. This has led to an increased interest in noninvasive endpoints for comparative trials. This study describes the history and possibilities of ST-segment recovery analysis as an endpoint in acute myocardial infarction trials. **Key words:** acute myocardial infarction, clinical trials, ST-segment, continuous monitoring, noninvasive patency assessment.

Traditional Endpoints

Traditional acute myocardial infarction (AMI) trials have used morbidity and mortality as endpoints. These endpoints occur relatively infrequently during the observation period and require large study populations. Left ventricular function and angiographic infarct-related artery patency have, therefore, been used as alternative endpoints. These assessments are costly, risk-laden, and put a large demand on resources not available in every hospital. Furthermore, the relationships among patency, left ventricular function, and mortality have not yet been resolved.[1–3] This has led to an increased interest in noninvasive endpoints for comparative trials.[4,5]

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Static Electrocardiographic Methods: Surrogate for Angiography

Observations of marked ST recovery at the moment of angiographically documented reperfusion led to several studies correlating quantitative ST recovery to infarct-related artery patency. Several methods comparing ST-segment deviation between a post-treatment electrocardiogram (ECG) and a fixed pretreatment reference ECG have been reported.[6–11] These methods measure the ST-segment deviation in one or a few post-treatment ECGs at intervals typically 60–180 minutes after onset of thrombolytic

Table 1. Sensitivity for Failed Reperfusion, Specificity, and Accuracy as Reported by Five Methods

Method	Sensitivity (%)	Specificity (%)	Accuracy (%)	n
von Essen et al.[6]	100	100	100	56
Hogg et al.[7]	67	93	88	17
Saran et al.[8]	43	97	80	45
Clemmensen et al.[9]	80	88	85	53
Hohnloser et al.[10]	95	84	87	82

These methods measure ST-segment recovery in a post-treatment ECG as a fractional change of a fixed, pretreatment reference ECG ST level. n = number of patients included in the study.

treatment. If the ST-segment has recovered below a threshold expressed as a fractional change of a fixed, pretreatment reference ECG ST level, reperfusion is considered to have occurred. If the ST-segment did not recover below this threshold, reperfusion is considered to have failed. Reported sensitivity for occluded infarct-related arteries, and the specificity and accuracy for five of these methods are listed in Table 1.

Continuous ST-Segment Monitoring: Real-time Triage and Beyond Angiographic Surrogate

Continuous ST-segment monitoring using Holter recorders was developed to better document the timing of reperfusion. Recordings were analyzed retrospectively and distinguished patients with reperfused infarct-related arteries from those in whom the infarct-related artery failed to reperfuse after treatment.[7–12] Holter recordings are limited in the amount of leads used and accessibility at the bedside for guidance of clinical care. Subsequently, a real-time oriented, digital 12-lead electrocardiograph was developed that makes continuous registration of the ST-segment deviation over time in all leads accessible at the bedside. Essentials of this ST monitor (ST100, Mortara Instrument, Milwaukee, WI) have been previously published.[13,14] Briefly, the ST monitor acquires and digitizes a 12-lead ECG every 20 seconds. The first acquired ECG is used as a reference for subsequent comparison of ST-segment amplitudes measured 60 ms after the J point. If subsequent ECGs show a persistent change in ST-segment deviation over 1 minute more than a preset threshold, normally 200 μV in a single lead or 100 μV in two leads, the violating ECG and an additional eight ECGs are stored over a 3-minute episode. An audible alarm warning the clinician of this ST change is optional. Trendlines of ST-segment deviation over time and full disclosure 12-lead ECGs on hard-copy are immediately available at the bedside. The last acquired ECG then serves as an updated reference ECG for ST-segment comparison. In the absence of ST-segment deviation changes an ECG is stored every 20 minutes by default. A similar device recording vectorcardiograms continuously has been developed in Sweden (Ortivus Medical Laboratories, Taby) and is also commercially available.[15]

Reports using continuous ST-segment monitoring have indicated that 25–50% of patients treated with intravenous thrombolytic therapy show unstable ST-segment recovery suggesting cyclic reperfusion of the infarct-related artery.[16–19] A new method of ST-segment recovery analysis using updated reference ECGs over multiple "peaks" and "troughs" was therefore developed to allow patency assessments not only during the phase of stable ST-segment recovery, but also in real time during the unstable, early phase prior to and immediately after initiation of thrombolytic treatment.[20] Details of this algorithm have been previously described.[21] During periods of increasing ST-segment elevation, the reference ECG is continuously updated to the ECG with the most ST-segment elevation. ST-segment recovery of ≥50% from this most abnormal or peak reference ECG is used to define periods of reperfusion. During such periods of ST-segment recovery, the reference ECG is continuously updated to the ECG with the least ST-segment elevation. Subsequent ST-segment reelevation of ≥150 μV in two leads or ≥200 μV in one lead, relative to this most normalized or trough reference ECG, is used to define periods of recurrent occlusion. Subsequent peaks and troughs are used as continuously updated reference points over the entire ST monitor recording.

This method of continuously updated ST-segment recovery analysis was tested in the thrombolysis and angioplasty in myocardial infarction 7 (TIMI) trial against simultaneous angiography in 144 patients.[22] Of the patients with TIMI grade 3 flow, 94% showed ST-segment recovery by the time of angiography. This was reduced to 81% in patients with TIMI grade 2 flow. Fifty-seven percent of the patients with TIMI

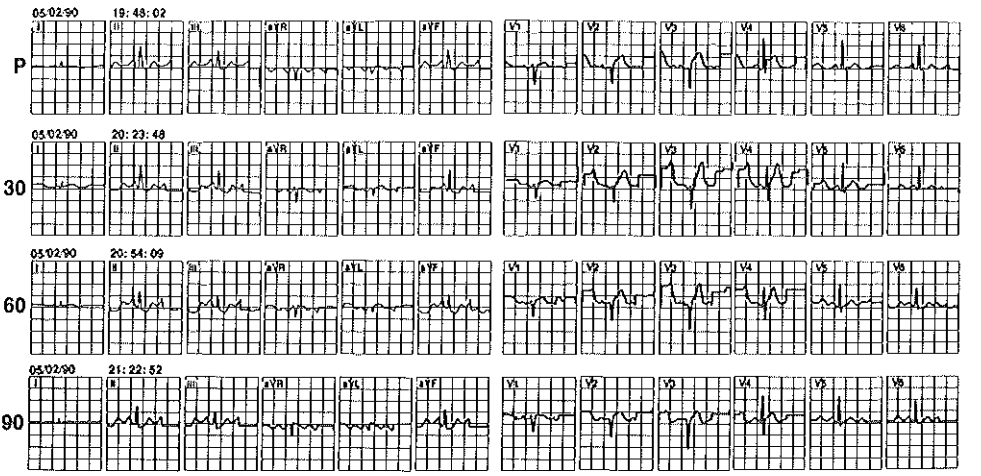

Fig. 1. Serial 12-lead ECGs recorded every 30 minutes from a patient presenting with an acute myocardial infarction of the anterior wall. ST-segment deviations in the peak lead (V_3) from consecutive post-treatment ECGs are compared with the fixed reference ST level of 5.8 mm measured in the pretreatment ECG (P). At 30 and 60 minutes, ST levels are 7.7 and 6.6 mm, respectively, and at those moments the infarct-related artery is considered to have remained occluded. At 90 minutes, the ST level is 2.6 mm, a 65% recovery from the pretreatment reference ST level, suggesting reperfusion. From Krucoff et al.[22] With permission.

grades 0–1 flow with collateral blood flow to the infarcted area showed ST-segment recovery, while this was true for only 11% of patients without collateral support. This spectrum suggests that ST-segment recovery can give physiologic information on successful reperfusion of the infarct area that is more than just a surrogate for the somewhat controversial gold standard of angiographic patency.

When assessments are performed during the more stable phase of ST-segment recovery, the method of continuously updated ST-segment recovery analysis appears to be as accurate as the methods comparing ST-segment deviation between a post-treatment ECG and a fixed, pretreatment reference ECG. As can be seen in Figures 1 and 2, the use of continuously updated reference ECGs instead of a fixed, pretreatment reference ECG seems to give important additional information during the earlier phase after thrombolytic treatment when cyclic flow is present.[22,23]

Cumulative Parameters of ST-Segment Recovery: From Reperfusion Physiology to Clinical Outcome?

As previously described,[21] continuously updated ST-segment recovery analysis allows cumulative assessments over the early phase of treatment, providing documentation of the speed and stability of reperfusion for comparison between drug regimens. Speed of reperfusion is defined as the time from the onset of thrombolytic treatment to the first evidence of 50% ST-segment recovery from an updated, peak reference ECG. Stability of reperfusion is reflected in the number of reocclusion and reperfusion events over the course of the infarction. The patent physiology index reflects the overall success of reperfusion therapy and is defined as the total duration of ST-segment recovery intervals as a percentage of the monitoring period. Parameters of speed and stability of reperfusion are currently being used in the ST monitoring substudy of the Global Utilization of Streptokinase and tPA for Occluded arteries (GUSTO) trial to elucidate differences in four different thrombolytic regimens. The ongoing registration of the onset and stability of reperfusion allows a nonvasive triage to select patients with failed or unstable reperfusion for trials that test the value of more aggressive secondary treatment strategies.

More quantitative approaches in addition to the detection of patency of the infarct artery or the determination of speed and stability of reperfusion are being sought. Serial precordial mapping studies performed by Maroko and Braunwald's group in the 1970s provided the first correlations between the se-

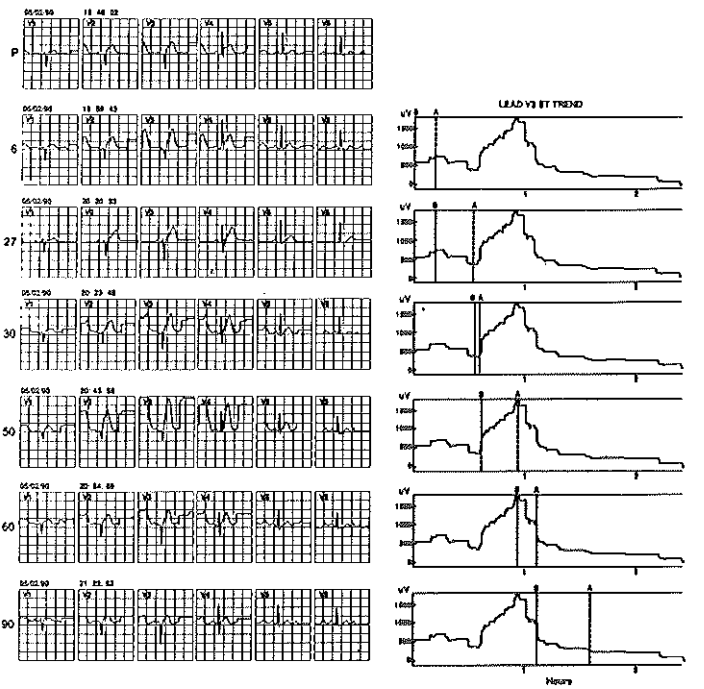

Fig. 2. Continuously updated ST-segment recovery analysis in the same patient as shown in Figure 1. Trends of summated ST-segment deviation over time, at right, with markers indicating the timing of selected ECGs, at left, as well as the updated reference peak or trough. The reference ST level is continuously updated as ST-segment elevation of 5.8 mm in lead V_3 of the pretreatment ECG (P) gradually worsens to 7.5 mm by 6 minutes after the onset of therapy. From this reference peak, ST-segment recovery to 3.7 mm (or 50%) 27 minutes following the onset of therapy suggests reperfusion of the infarct-related artery. From this updated reference trough, rapid reelevation over 3 minutes to 7.7 mm in the same fingerprint pattern suggests recurrent occlusion, with progressive ST-segment elevation to the true maximum peak of 18 mm elevation at the peak 50 minutes after the onset of therapy. Using this latest peak as an updated reference for further comparison, ST recovery of >50% occurs 10 minutes later when the ST level is 6.6 mm, suggesting that the infarct-related artery has again become patent. Thus, while the analysis using a static pretreatment reference ST level only detects the onset of reperfusion 90 minutes following the onset of therapy (Fig. 1), the continuously updated ST-segment recovery analysis method identifies two reperfusion episodes: the first one starting 27 minutes following the onset of therapy and the second one starting 60 minutes following the onset of therapy. From Krucoff et al.[22] With permission.

verity and extent of ST-segment deviation with myocardial mass at risk and clinical outcome.[24] Barbash and co-workers correlated acute ST-segment recovery with the salvage of myocardium and showed that acute ST-segment recovery was a strong predictor of favorable clinical outcome.[25] The severity of ischemia is generally determined as the amount of ST-segment elevation seen on the acute ECG. Continuous monitoring might improve the definition of the maximum amount of ischemia in patients with cyclic reperfusion in whom a single or few static ECGs were taken during periods of actual ST-segment recovery. The detection of the extent of the ischemic area reflected in the number of leads with ST-segment deviation could be similarly improved. The integration of the dynamics in the severity and extent of ischemia over time as a time-severity index provide an exciting potential to elucidate the response to treatment as a relationship among infarct-related artery patency, the amount of myocardium salvaged, and clinical outcome. Developing such a model will require a thorough process of statistical modeling or neural network development that includes other routinely available noninvasive descriptors to yield a practical probabilistic, patient-specific, prediction of infarct outcome.

Overview

Continuously updated ST-segment recovery analysis in conjunction with frequent electrocardiographic acquisition allows accurate, noninvasive assessment of the perfusion status of the infarct area. ST-segment recovery strongly correlates with perfusion either through the infarct artery or through collateral blood supply. Lack of ST-segment recovery has consistently been correlated with failure to reperfuse the infarct-related artery or the more severely depressed left ventricular function.[6–12,16,18,19,21–23,25] Continuous registration of ST-segment deviation allows the registration of the onset and stability of reperfusion, and thus, gives more information than "snap-shot" assessments made with coronary angiography. Noninvasive identification of failed or unstable reperfusion using continuously updated ST-segment recovery analysis can be useful in trials testing the value of more aggressive secondary revascularization strategies for these selected subgroups.

Continuous ST monitoring is applicable in the majority of patients. It has not yet been validated in patients with delayed ventricular conduction, but that comprises a small part of the population. More restricting is the requirement that initial ST-segment deviation reflective of coronary occlusion be present when ST monitoring is initiated. This is a common source of anatomic bias, favoring anterior above inferior infarctions and both above posterior infarctions. This also requires that ST monitoring be initiated in an early phase, preferably before treatment. The availability of hard-copy ECGs recorded during coronary occlusion can substitute missing ST monitoring data in the early phase to assess patency, but this limits the detection of the onset and stability of reperfusion. Combinations of ST monitoring with other noninvasive markers of reperfusion, such as enzyme measurements, need to be investigated.[23,26–30] While these markers do not provide a cumulative assessment of reperfusion status over time, they might improve the accuracy of ST monitoring. They can substitute ST monitoring in patients where ST monitoring is not feasible due to the absence of an injury current or the presence of confounding factors.

In this era clinicians can choose from a wide therapeutic arsenal of intravenous and intracoronary thrombolytic treatments—mechanical revascularization, emergency coronary bypass operation, anticoagulant and antiplatelet therapy, perfusion and oxygenation assist devices—and many additional forms of pharmacologic treatments to modify the natural course of AMI. However, the value of these strategies needs to be compared and should be optimized for individual patients. An accurate noninvasive marker of reperfusion, such as ST monitoring with the additional benefit of cumulative assessments over time, can serve as a noninvasive tool. It is easy to apply and is a relatively inexpensive endpoint for comparative trials for AMI, and can enhance the understanding of the underlying physiology.

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Chapter 8

The Impact of Autoperfusion on Quantitative Electrocardiographic Parameters of Ischemia Severity, Extent, and "Burden" During Salvage of Elective Coronary Angioplasty

The Impact of Autoperfusion on Quantitative Electrocardiographic Parameters of Ischemia Severity, Extent, and "Burden" During Salvage of Elective Coronary Angioplasty

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ABSTRACT: Long angioplasty inflations have been reported using an autoperfusion system that delivers oxygenated blood distal to the balloon segment. The safety and efficacy of this system has been demonstrated in anatomically selected patients. The clinical use, however, is frequently to stabilize intimal dissection in unselected patients. We reviewed 12-lead continuous electrocardiographic (ECG) recordings in 40 patients in whom prolonged salvage with autoperfusion was attempted. Sub-optimal results were stabilized in 36 of 40, while 4 patients had urgent bypass. The presence of ischemia, as ≥ 100 uV ST elevation over the 12 lead ECG, and the total ST deviation over all leads over the entire inflation period (total ischemic "burden") were compared within each patient between the longest standard balloon and autoperfusion inflations. Median duration of inflation was 3.03 min. with balloon vs. 15.6 min. with autoperfusion ($p < 0.00002$). Of the 40 patients, 35 (87%) had ECG ischemia with balloon vs. 18 (45%) with autoperfusion ($p < .00002$). Median severity of peak ST deviation was 321 uV with balloon vs. 132 uV with autoperfusion ($p=0.0001$). Median extent of ST elevation was 3 leads with balloon vs. 0 leads with autoperfusion ($p=0.0001$). Median total ischemic burden was similar with balloon (1173 uVmin) and autoperfusion (1083 uVmin, NS) despite the fivefold longer inflation duration with autoperfusion. Thus, in patients selected by clinical necessity rather than optimal anatomy, severity and extent of ST elevation were significantly reduced, although not entirely eliminated, by autoperfusion.

J INVAS CARDIOL 1994;6:234-240

Key words: coronary angioplasty, myocardial ischemia, ST-segment

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Prolonged balloon inflations are widely used to stabilize intimal dissection and avoid urgent bypass surgery when shorter balloon inflations produce sub-optimal angioplasty results.[1-5] While brief interruption of coronary flow is gen-

erally well tolerated, ischemia from longer balloon inflations may be complicated by severe chest pain, hypotension, or arrhythmias from the resultant metabolic perturbation of myocyte metabolism.[6,7]

Autoperfusion of the myocardium distal to the dilatation site has been described using a balloon catheter (Stack Perfusion Balloon Catheter™, Advanced Cardiovascular Systems, Inc., Santa Clara, California) with side holes cut through to the center lumen proximal and distal to the balloon segment.[8-14] When the guidewire is withdrawn, the difference between mean arterial blood pressure and mean coronary wedge pressure drives oxygenated red blood cells into the center lumen, exiting distal to the inflated balloon, perfusing the myocardium at approximately 60 cc/min. The safety and efficacy of autoperfusion with this device has been described in selected patients.[8-14] The impact of autoperfusion on ischemia in an unselected population in whom the autoperfusion balloon is used clinically to salvage sub-optimal angioplasty results has never been quantified.

Continuous multi-lead ST segment monitoring provides a comprehensive electrocardiographic record for the objective quantification of ischemia during transient coronary occlusion.[15-17] From a database of elective angioplasty patients undergoing ST-segment monitoring, electrocardiographic parameters of ischemia were reviewed in all patients in whom autoperfusion was secondarily used to improve a sub-optimal angioplasty result following dilatation with a standard balloon catheter. With each patient serving as their own control, parameters of ST-segment deviation were compared between periods of standard balloon occlusion and autoperfusion at the same coronary artery site to quantitatively assess the impact of autoperfusion on procedural ischemia.

METHODS

Patient Population. All patients were referred for elective angioplasty based on routine clinical indications in our institution. The patients included in this study were retrospectively identified from the Ischemia Monitoring Laboratory database. Patients in the Ischemia Monitoring Laboratory database represent an unselected subset of our total elective interventional population, up to the limits of the ST-monitoring equipment available. Patient selection criteria for this study included all of the following: complete 12-lead ST monitor data from the angioplasty procedure; normal conduction on baseline electrocardiogram (ECG); standard balloon selected primarily; identical lesion also dilated with an autoperfusion balloon for "salvage" during the same procedure.

Angioplasty. All patients were premedicated with 325 mg aspirin and 10,000-12,000 units of intravenous heparin prior to the start of the procedure. Angioplasty equipment selection, including the use of autoperfusion, and the duration of balloon inflations were solely at the discretion of the operator's clinical judgement. In all patients, autoperfusion was accomplished with the Stack Perfusion Balloon Catheter. Angiographic "success" was defined as a final luminal stenosis that was both a >20% reduction of the pre-angioplasty lesion and a final luminal narrowing of ≤50% based on visual consensus assessment between 2 or more operators.

ST-segment monitoring. All patients were monitored with a digital 12-lead electrocardiographic monitor (Mortara ST-100 Monitor, Mortara Instrument, Milwaukee, WI) as has been described previously in detail.[18-19] In summary, this device acquires a standard digital 12-lead ECG every 17-20 seconds. All ECG data are downloaded to a PC computer for retrospective analysis using custom written software.[14,15] Full disclosure, superimposition scanning of all ECG's and 3-dimensional graphic display of ST-segment levels, measured 60 milliseconds beyond the J-point, across the precordium trended over time (Figure 1) were used for scanning of all patient studies.

Catheterization laboratory clock times and diary sheets indicating periods of balloon inflation and deflation as well as device used are synchronized routinely with the digital clock times of the ST-segment monitors for the Ischemia Monitoring Laboratory database. From these synchronized periods, the longest standard and longest autoperfusion balloon inflation periods were identified within each patient for further quantitative analysis and comparison. In all cases, inflations were compared only for angiographically identical coronary site occlusions by both the standard and the autoperfusion balloons.

From each study, three ECGs of interest were identified as part of the quantitative analysis: the pre-procedure baseline; the pre-deflation of maximally abnormal ECG during the longest standard ballon inflation (peak PTCA); and the pre-deflation or maximally abnormal ECG during the longest autoperfusion inflation (peak

PBC). Identification of all "peak" deviation ECGs and all measurements of deviation were taken as relative to, or the "delta" from each patient's own baseline ST levels for each of the 12 leads.

Electrocardiographic parameters of ischemia were quantified by comparing the amount of change between the baseline and peak PTCA ECG to the amount of change between the baseline and the peak PBC ECG. Electrocardiographic "ischemia" was defined as ≥100 uV of new ST elevation in at least 1 lead. Three electrocardiographic parameters were retrospectively analyzed, as summarized in Figure 2. "Severity" of ischemia was defined by the peak amplitude of ST deviation in the most deviated single lead out of the standard 12–leads. "Extent" of ischemia was taken as the total number of leads over the precordium showing ≥100 uV of new ST–segment elevation. "Total ischemic burden" was taken as the total summated absolute ST–segment deviation over all 12 leads over the entire duration of each balloon inflation (calculated as the area under the trend of 12–lead ST deviation from baseline over time). In each case, these ECG parameters were examined as changes only relative to other ECG measurements with each patient serving as their own control. No attempts were made to relate the severity, extent, or total "burden" parameters of ischemically mediated quantitative ECG changes to myocardial mass or any non–ECG measure.

Statistical analysis. All analyses were performed on the change in the ECG measures from the standard balloon inflation to the autoperfusion inflation with each patient serving as their own control. A Wilcoxon signed rank test was used for "severity," "extent," and "burden" to evaluate whether or not these changes were significantly different from zero. McNemar's test was used to test for agreement in occurrence of ischemia between the two dilatation methods. All continuous variables are presented as medians and quartile ranges (25th-75th percentiles). All categorical

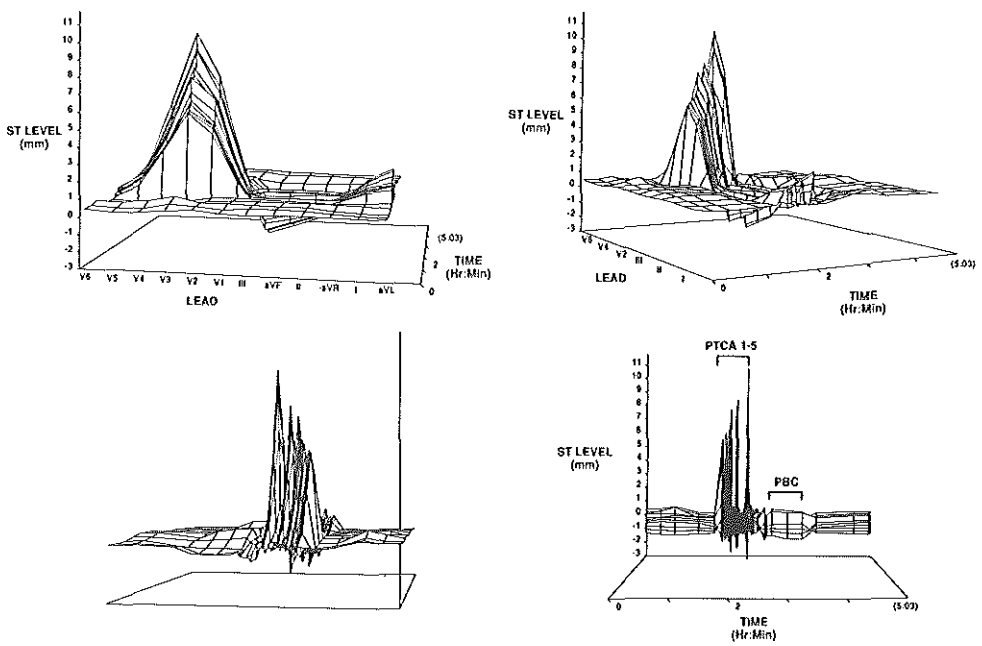

Figure 1. *Four spatial rotations of graphic depiction of ST segment level (y–axis, or "severity") for each of the 12 leads monitored (X–axis, or "extent") continuously over 5 hours time (Z–axis) in a patient during standard balloon (PTCA) inflations and then autoperfusion (PBC) inflation to salvage LAD angioplasty threatened by unstable intimal dissection. Five balloon inflations (PTCA 1-5) ranging serially from 1.5 to 5 minutes produced 5-11 millimeter ST elevation but did not stabilize dissection. A 30 minute autoperfusion inflation (PBC) was tolerated with little ischemic ST deviation, and produced a stable final result.*

variables are presented as number of patients with the event or characteristic. For the number of tests run on this small population, the p–value considered significant was adjusted to ≤ 0.0125.

RESULTS

A total of 40 patients meeting all criteria were identified from our database. Patient characteristics are shown in Table 1. In all cases the operator switched from a standard balloon system to a perfusion balloon system to salvage a sub–optimal result or an unstable intimal dissection. In 36 of the 40 patients a successful end result was achieved, while in 4 patients urgent coronary bypass grafting was subsequently performed. In all 4 of these patients the deflated perfusion balloon was left across the stenosis en route to the operating room.

Ischemic ST elevation in at least 1 lead occurred in 35 of the 40 patients (87%) during standard balloon inflation. During autoperfusion only 18 of the 40 (45%) had ischemic ST elevation ($p < 0.00002$). The median duration of the longest balloon inflation was 3.0 minutes (1.6, 4.0 minutes) for standard angioplasty and 15.6 minutes (15.0, 23.0 minutes) for autoperfusion ($p < 0.00002$).

Electrocardiographic parameters of ischemia with and without autoperfusion are shown in Figure 3. The median severity of ST deviation during angioplasty was 321 uV (188,468 uV), compared to 132 uV (70,183 uV) during autoperfusion ($p < 0.0001$). The range of peak ST deviation from baseline was 42-1837 uV during angioplasty and 28-568 uV during autoperfusion. The median ECG extent of ischemia as number of leads showing > 100 uV deviation from baseline during standard balloon inflation was 3.0 leads (3.0, 6.0 leads), compared to 0 leads (0.0, 3.0 leads) during autoperfusion ($p<0.0001$). The range of leads deviated was 0-7 for both. The median total "burden" of ischemia during the longest standard balloon inflation was 1173 uVmin (698-1683 uVmin), compared to 1083 uVmin (560, 1360 uVmin) during the longest autoperfusion dilata-

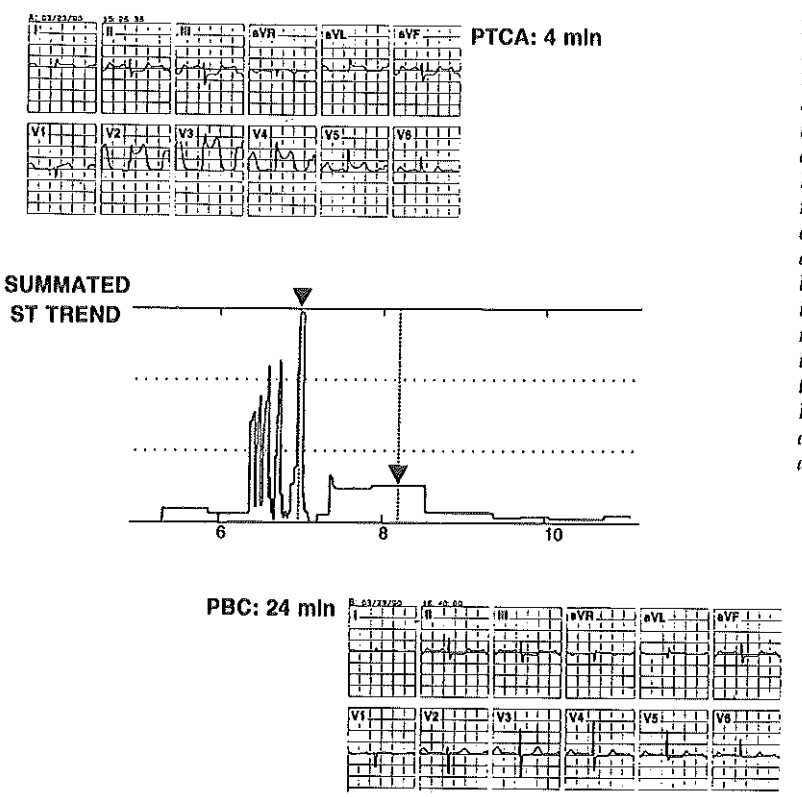

Figure 2. *Analogue ECGs and a trend of 12–lead summated ST deviation over time, from the case described in Figure 1. ECG "A" shows 11 millimeter anterolateral ST elevation during standard balloon inflation. While ischemia over the 30 minute autoperfusion inflation is visible in the summated trend, ECG "B" shows only diffuse ST depression after 24 minutes.*

Table 1. Baseline Characteristics

DESCRIPTOR	Number (%)	(25th, 75th Percentile)
Age (years)	59	(53, 66)
Male Sex	28 (68)	
Vessel disease:		
1 vessel	17 (43)	
2 vessel	14 (35)	
3 vessel	9 (22)	
Artery dilated:		
LAD	17 (43)	
Circumflex	7 (17)	
Right	16 (40)	
Stenosis:		
pre–PTCA	95	(75, 95)
post–PTCA	25	(15, 38)
Dissection post–PTCA	27 (67)	
Successful post–PTCA	37 (93)	
Complications:		
None	36 (90)	
Urgent bypass	4 (10)	
Death	0	

tion (NS). The range of ischemic burden was from 181 to 4,581 uVmin during standard angioplasty compared to 110 to 6561 uVmin during autoperfusion. As defined, ischemic burden included the entire duration of the longest dilatation, and so was acquired over a fivefold longer period for the autoperfusion inflations compared to the longest standard balloon inflations.

DISCUSSION

Elective selection of patients for long autoperfusion dilatations has focused on more proximal, focal sites not contiguous with large side branches[8-14], and the safety and efficacy of autoperfusion in such patients is well demonstrated.[8-14] In clinical application, however, the autoperfusion system is generally used to salvage unstable angioplasty results. In many such patients, standard balloons are initially selected due to some anatomic constellation that is considered relatively unfavorable either for the delivery of or for the function of the autoperfusion system. Our patients were further subselected by the change of the elective procedure to a "salvage" situation, as indicated by the median standard balloon inflation duration of around 3 minutes and the 10% acute bypass surgery incidence even with the use of autoperfusion. While this "salvage" application represents the most common clinical use of the device, to our knowledge there was no data in the literature showing that autoperfusion actually reduced ischemia when used with clinical urgency.

Using each patient as their own control, our data show that using autoperfusion a five–fold increase in the inflation time for salvage of the dilatation site was obtained with a reduction in most quantitative ECG parameters of ischemia, including a trend towards reduction of the total ischemic "burden" of ECG deviation despite this prolongation of the inflation time. In 45% of patients there was no detectable ST elevation across the 12–lead ECG during autoperfusion. In most patients, however, some ischemic ECG changes did occur. Total ischemic burden accrued over 15 minutes of inflation using autoperfusion was similar to that which accrued over 3 minutes with standard balloon inflation.

There are several noteworthy limitations to our data. As a retrospective analysis taken from the Ischemia Monitoring Laboratory database, more precise or prospective information on why a standard balloon was initially selected by each operator is not available. In addition, not all autoperfusion salvage cases were recorded with 12-lead ECG monitors, hence these 40 patients represent only a subset of our total clinical "bailout" use of autoperfusion. ECG parameters of ischemia "extent," "severity" and total "burden" in this study are not correlated with ventricular dysfunction, myocardial mass or any non–ECG measures.

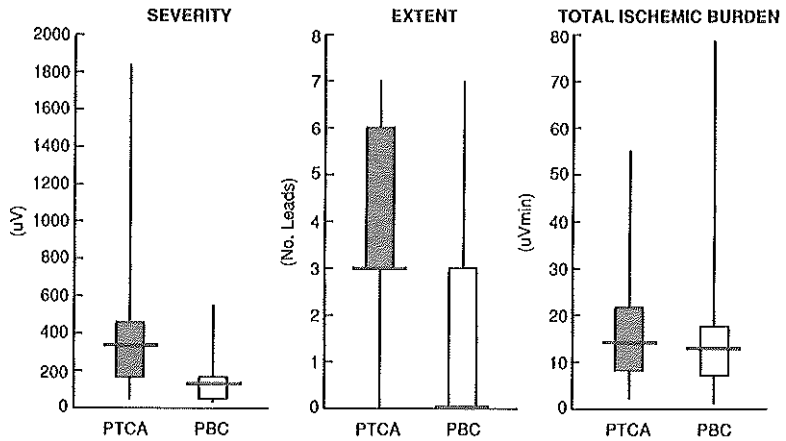

Figure 3. *Median, 25th, 75th percentile, and range for standard balloon (PTCA) and autoperfusion (PBC) inflations are shown for each of the 3 quantified ECG parameters: ischemia severity, extent, and total ischemic burden. See text for detail.*

Finally, it has been observed in some patients that multiple conventional balloon inflations may cause "fading" of ischemia onset or preconditioning of the myocardium[16] and in all of our cases the autoperfusion inflations were subsequent to the standard balloon inflations. Despite these limitations, however, it can be pointed out that these cases evolved with the truly unpredictable nature of the real world practice of angioplasty, within a population undergoing ST-segment monitoring with no discrete bias as to case selection other than a standard balloon was selected initially. Our 40 cases represent 100% of the relevant cases in our data base. The ECG parameters, although not referenced per se to a non-ECG measure, were all analyzed using each patient as their own control, and so represent a fairly robust means of detecting anti-ischemic effects, as demonstrated by the statistical power of the observations despite the relatively small number of patients overall and the adjusted significance level used for p values. Finally, while preconditioning effects are measurable in human patients, the ability to achieve a five-fold increase in dilatation time with reduction in all quantitative ECG parameters is, in our opinion, unequivocal objective evidence of nutritive blood flow through the autoperfusion system in this setting.

"Severity" of ischemia conceptually reflects the progress from reversible to irreversible cellular injury inflicted by continued metabolic demand in an oxygen deprived environment.[20] Over this spectrum, more complete or more prolonged interruption of blood flow results in a more rapid and complete inability to actively maintain trans-membrane ionic gradients, resulting in focal potassium leakage reflected electrocardiographically by progressive amplitude of ST elevation. In Figure 1, standard balloon inflations in the same patient at the same coronary site produce from 5 millimeters ST elevation during a 2 minute inflation to 10.7 millimeters elevation during a 5 minute inflation. The marked reduction of peak ST segment deviation and the elimination of any ST elevation during a 30 minute inflation with autoperfusion most likely reflects the ability of the device to deliver metabolically nutritive blood flow to the distal myocardium even in this semi-urgent application.

More "extensive" ischemia conceptually reflects the geographic mass of myocardium insulted, either by a more proximal stenosis, a stenosis in a larger artery, or in a setting where multiple territories might be simultaneously affected. More extensive ischemia as electrocardiographically demonstrated by more widespread lead activity over the precordium has been associated with greater left ventricular dysfunction during coronary occlusion.[21] The marked impact of autoperfusion in our patients in reducing the number of leads with ST elevation is particularly interesting since occlusion of an important side branch by the perfusion balloon segment would still be likely to produce ST elevation somewhere on a 12-lead ECG. The median number of leads showing ST elevation during autoperfusion was zero in our patients, suggesting that adequate positioning was achievable in most patients despite the fact that initial decisions to use standard balloons may have reflected anatomic concerns about side branches.

Total "burden" of ischemia conceptually inte-

grates the severity and extent of the metabolic derangement as accumulated over time. The clinical or intuitive appreciation of the impact of autoperfusion on this parameter is reflected by the clinical operator decisions leading to the five-fold longer inflation times during autoperfusion. Objectively, the ability to prolong inflation time without increasing the electrocardiographic ischemic burden supports the ability to mechanically stabilize dissected coronary intima using longer dilatation times. It is equally noteworthy, however, that while ischemia was reduced to the point of improved tolerance, it was not entirely eliminated.

The perfusion balloon catheter continues to evolve as a flexible tool for angioplasty. Considerable data has shown that the perfusion balloon catheter provides excellent procedural tolerance in selected patient populations.[8-14] In addition, our data show evidence of the metabolic effectiveness of this device in the semi-urgent salvage of angioplasty procedures, as is common to the clinical use of the device. The longer dilatations used to stabilize such intimal dissections were accompanied by significant reduction in quantitative electrocardiographic parameters of ischemia even in this population whose anatomy was initially considered potentially unfavorable for autoperfusion.

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Chapter 9

Comparison of Continuous ST-Segment Recovery Analysis with Methods Using Static Electrocardiograms for Noninvasive Patency Assessment During Acute Myocardial Infarction

Comparison of Continuous ST-Segment Recovery Analysis with Methods Using Static Electrocardiograms for Noninvasive Patency Assessment During Acute Myocardial Infarction

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Continuous ST-segment recovery analysis and 5 static methods using ST-segment comparison between a pre- and post-treatment electrocardiogram were compared for their ability to predict infarct-related artery patency in 82 patients with acute myocardial infarction who underwent angiography a median of 124 minutes after onset of thrombolytic treatment. Accuracy at the moment of angiography was 85% (95% confidence interval [CI] 77% to 93%) for the continuous method, and 68% (CI 57% to 78%), 78% (CI 69% to 87%), 83% (CI 74% to 91%), 82% (CI 73% to 90%), and 80% (CI 71% to 89%) for the static methods. At the moment of angiography the most accurate static method and the continuous method agreed in patency assessment in 90% of the patients (CI 84% to 97%). Agreement was reduced to 83% (CI 75% to 91%) of patients when a patency assessment was performed earlier at 90 minutes after treatment onset, and was only 77% (CI 68% to 86%), at 60 minutes. Early disagreement was mainly seen when the continuous ST recording showed ST recovery from a delayed peak ST elevation after the pretreatment static electrocardiogram or when dynamic ST changes suggesting cyclic reperfusion occurred. Continuous ST-segment recovery analysis appears to be as accurate as the most accurate static methods. Continuously updated reference points appear to give important additional information when ST recovery follows a delayed peak ST elevation or when reelevation occurs, suggesting cyclic flow changes. Such findings appear to affect about half of patients with acute myocardial infarction treated with intravenous thrombolysis, particularly early after administration of therapy.

(Am J Cardiol 1994;73:1069–1074)

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Patients with acute myocardial infarction in whom coronary patency is not restored after intravenous thrombolytic therapy may benefit from additional pharmacologic or mechanical therapy.[1–10] Because it is not feasible to subject all patients to acute coronary angiography, an accurate noninvasive patency assessment method is desirable. Several methods using assessment of ST-segment recovery between a single pretreatment electrocardiogram and ≥1 static post-treatment electrocardiogram have been correlated with infarct-related artery patency.[11–15] However, only 1 study included simultaneous electrocardiographic and angiographic assessments. More recently, continuously updated ST-segment recovery analysis for real-time noninvasive patency assessment has been reported using digital ST monitors.[16–18] It uses a continuous stream of 12-lead electrocardiograms, recognizing true maximal and minimal ST deviations as they occur rather than making assessments at static intervals.[16–20] The added demand for a dedicated ST monitor and use of a more complex algorithm must be weighed against simpler static methods. This retrospective study assessed such differences in a single population of patients with acute myocardial infarction, including those differences at the moment of simultaneous angiography.

METHODS

Patient population: One hundred forty-four patients from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 7 trial with ST monitoring and acute coronary angiography as previously described[18,21] were considered for this study. Briefly, patients presenting within 6 hours after symptom onset, without contraindications for thrombolytic therapy, and able to give informed consent were eligible. Enrollment in the TAMI 7 trial required ST elevations of ≥100 μV measured 0.02 second after the J point in (1) 2 inferior leads, (2) 2 precordial leads, (3) leads I and aVL, or (4) ST depression of the precordial leads consistent with posterior infarction. Patients were not enrolled if they had evidence of a previous Q-wave infarction in the same area of ST elevation. Patients received "front-loaded" regimens of recombinant tissue-type plasminogen activator and acute catheterization per the TAMI 7 protocol.[21] Thirty-four patients whose ST monitoring was initiated >30 minutes after onset of thrombolytic treatment were excluded from this study. In addition, 10 patients were excluded because

a pretreatment electrocardiogram was missing, and 18 more were excluded whose ST monitoring was interrupted or confounded by noise or transient conduction abnormalities for >30 minutes before catheterization. Thus, of the 144 patients with angiography and ST-segment monitoring in the TAMI 7 trial, all 82 who could be analyzed for the purposes of this study were included.

Angiography: Angiograms were analyzed at the core angiographic laboratory at the University of Michigan, where investigators were unaware of all electrocardiographic data after onset of therapy. As described previously,[18] angiographic patency was evaluated at the first contrast injection of the infarct-related artery. The Thrombolysis in Myocardial Infarction (TIMI) trial flow 0 to 1 was taken as occluded and TIMI flow 2 to 3 as patent. Collateral flow was not considered.

ST monitoring: All patients were connected to the digital 12-lead ST monitor previously described.[16] All electrocardiograms recorded with the ST monitor were transferred to a floppy disk for later analysis. An ST monitor electrocardiogram simultaneous to the first contrast injection of the infarct-related artery was printed out for the static electrocardiographic comparisons.

ST-monitoring analysis: Continuously updated ST-segment recovery analysis, the specific criteria and ability to predict infarct-related artery patency have been described in detail.[17,18] In contrast to static methods, during periods of ST-segment worsening, the reference electrocardiogram is continuously updated to the electrocardiogram with the most ST elevation. ST recovery of ≥50% from this most ST-elevated electrocardiogram is used to define periods of reperfusion. During such periods of ST recovery, the reference electrocardiogram is continuously updated to the electrocardiogram with the least ST elevation. Subsequent ST reelevation of ≥150 μV in 2 leads or ≥200 μV in 1 lead relative to this most ST-normalized electrocardiogram is used to define periods of recurrent occlusion. Subsequent points of maximal or minimal ST deviation are used as continuously updated reference points over the entire recording. Time

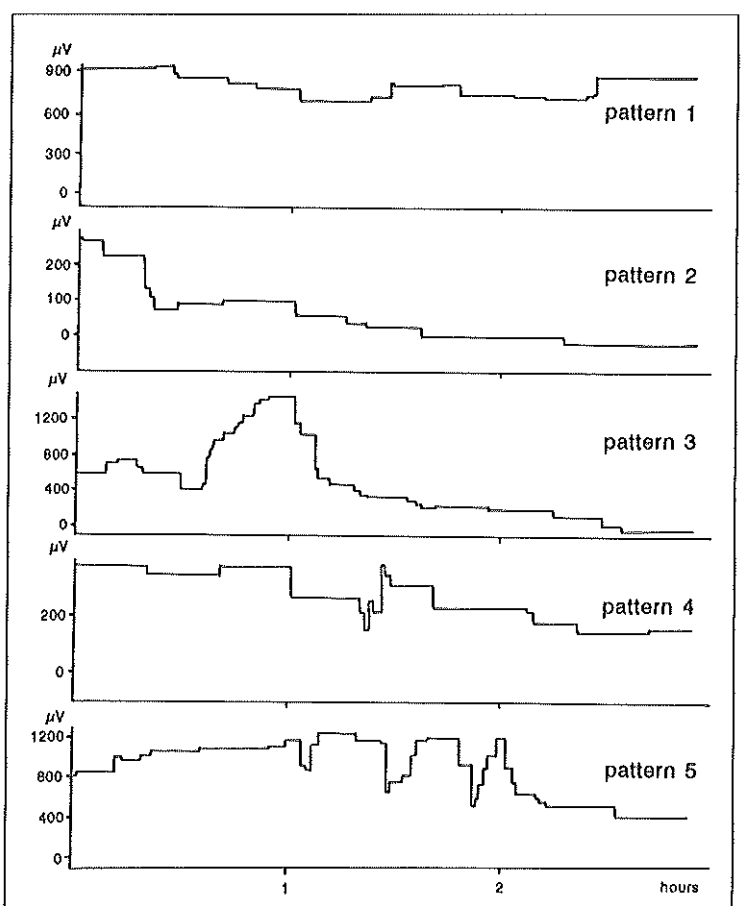

FIGURE 1. Five different patterns of ST recovery are identified on the continuous recordings before angiography: (1) continuing ST elevation, (2) ST recovery without reelevation, (3) ST recovery after a delayed peak (increased ST elevation after the pretreatment electrocardiogram ≥25%), (4) ST recovery followed by ≥1 ST reelevation episode, and (5) ST recovery after a delayed peak and followed by ≥1 reelevation episode.

TABLE I Description of Each of the Static Electrocardiogram Recovery Analysis Methods*

Method	Author	Leads	↑ / ↓	Measured	ST-Red. (%)	Time (min)
I	von Essen[11]	I, II, III	↑ and ↓	J + 60 ms	> 55	60
II	Hogg[12]	Worst lead	↑	J point	≥ 50	180
III	Saran[13]	Worst lead	↑	J point	> 25	180
IV	Hackworthy[14]	12 leads	↑	J + 40 ms	> 40	60, 120
V	Clemmensen[15]	11 leads	↑	J point	≥ 20	90

*Leads used to calculate the amount of ST recovery, measurement of only elevation or both elevation and depression, measurement point, percent recovery required for patent prediction, and time from onset of treatment to the stipulated moment of the patency assessment.
↑ = ST elevation; ↓ = ST depression.
Red. = reduction.

TABLE II Occlusion Detection Rate, Patency Detection Rate, and Accuracy for Each of the Static Methods (I to V) and for the Continuous Method*

Method	Sensitivity (%)	Specificity (%)	Accuracy (%)	Indet.
I	71 (52–91)	66 (53–79)	68 (57–78)	8 (10%)
II	63 (43–82)	84 (75–94)	78 (69–87)	1 (1%)
III	58 (39–78)	93 (86–100)	83 (74–91)	1 (1%)
IV	60 (41–79)	93 (86–100)	82 (73–90)	
V	48 (27–68)	93 (86–100)	80 (71–89)	2 (2%)
Continuous	64 (45–83)	93 (86–100)	85 (77–93)	

*The number of indeterminate predictions that were excluded from the denominator in each of the static methods are given in the far right column.
Indet. = indeterminate predictions.

TABLE III Number of Disagreements in Patency Assessments Between the Continuous Method and Static Method IV Listed According to Source of Disagreement and in Which ST-Recovery Pattern Group They Occur

Disagreement Source	Pattern	Minutes 60	Minutes 90	Angiography
Delayed peak	3, 5	14	10	4
Reelevation	4, 5	1	1	0
Threshold	1, 2	4	3	4
No disagreement (%)		63 (77) (68–86)	68 (83) (75–91)	74 (90) (84–97)

*Percentages of the total population and 95% confidence limits are given between brackets. See text for explanation.

from onset of thrombolytic therapy to first evidence of patency, the number of recurrent occlusions before angiography, and time to stable patency were recorded for each patient. Patency was considered stable if from that moment onward no recurrent occlusions occurred before angiography. Patients were then classified into 1 of 5 patterns of ST recovery (Figure 1), similar to those described by Dellborg et al.[20]

Static electrocardiogram methodology: All 5 published methods comparing static pre- and post-treatment electrocardiograms to predict infarct-related artery patency were selected for their ability to reproduce the method with available electrocardiograms.[11–15] Table I summarizes their essential features. Reported accuracies of these methods have previously been published.[22] Hard-copy electrocardiograms before therapy and at the moment of angiography were hand-measured as specified by each published method by an experienced technician unaware of all other data. Predictions of "patent" or "occluded" were determined for each patient using the threshold for ST recovery of each method. An "indeterminate" prediction was given if a method could not be applied owing to absence of the required ST deviation in the leads specified for measurement.

Data analysis: The ability to predict the angiographic status correctly was described as sensitivity, specificity, and accuracy. Sensitivity was defined as the number of patients correctly predicted as "occluded" as a percentage of the total number of patients with an angiographically occluded infarct-related artery. Specificity was defined as the number of patients correctly predicted as "patent" as a percentage of the total number of patients with an angiographically patent infarct-related artery. Accuracy of a patency assessment method was defined as the overall number of correct predictions as a percentage of the study population. Patients whose predictions were "indeterminate" owing to inapplicability of a static method were excluded from the denominator of that method. To determine the likelihood of interpretative differences over the course of early patient management, assessments of the continuous method and the most accurate static method at angiography were also compared at 60 and 90 minutes after onset of treatment. Disagreements were related to the overall ST recovery pattern registered with the ST monitor.

RESULTS

Eighty-two patients were included in this study, of whom 82% were men, with a median age of 56 years (quartile range 47 to 66). Age and gender distribution were not significantly different from the TAMI 7 patients not included in this study. Thrombolytic treatment was initiated a median of 156 minutes (quartile range 114 to 235) after symptom onset. First injection of contrast in the infarct-related artery occurred a median of 124 minutes (quartile range 93 to 163; range 20 to 336) after onset of thrombolytic therapy. The infarct-related artery was the left anterior descending in 37 patients (45%), left circumflex in 11 (13%), and right coronary artery in 34 (42%). Multivessel disease was seen in 41% of the patients. TIMI flow was grade 0 to 1 in 25 patients (30%), grade 2 in 13 patients (16%), and grade 3 in 44 patients (54%).

Sensitivity, specificity, and accuracy with which each method predicted infarct-related artery patency is listed in Table II. Method I considered limb leads only, and so

was indeterminate in 8 patients (10%) with isolated anterior ST deviation. In 3 other static methods, 1 or 2 patients were excluded as indeterminate because they only had ST depression, although the methods specified ST elevation. Ninety-five percent confidence intervals were wide, but sensitivity, specificity, and accuracy of the continuous method seemed equal to those of static methods II to V.

The frequency with which each of the 5 patterns of ST recovery occurred in this population is shown in Figure 2. Timing of ST evidence of patency, recurrent occlusions, and stable patency were highly variable and did not correlate with any suggested static assessment moment. Median time to first reperfusion was 40 minutes, ranging from 39 minutes before to 136 minutes after onset of thrombolytic treatment. At least 1 recurrent occlusion was seen in 32 patients, with a median of 1 and a maximum of 8 recurrent occlusion(s). Stable reperfusion was seen a median of 97 minutes (range 50 to 204) after onset of thrombolytic therapy.

The most accurate static method IV was compared with the continuous method at 60 and 90 minutes after onset of thrombolytic therapy in addition to the moment of angiography a median of 2 hours after onset of thrombolytic therapy. Table III shows the frequency of disagreement at each assessment time relative to the over-

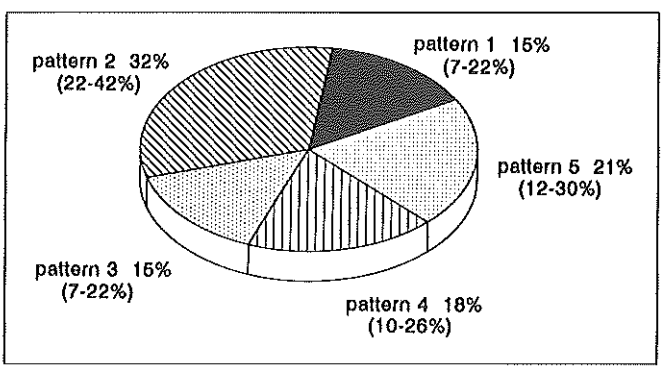

FIGURE 2. Occurrence of ST recovery patterns as (1) continuing ST elevation, (2) ST recovery without reelevation, (3) ST recovery after a delayed peak, (4) ST recovery followed by ≥1 ST reelevation episode, and (5) ST recovery after a delayed peak and followed by ≥1 reelevation episode. The percentage of the study population in each group is given, with the 95% confidence limits in *parentheses*.

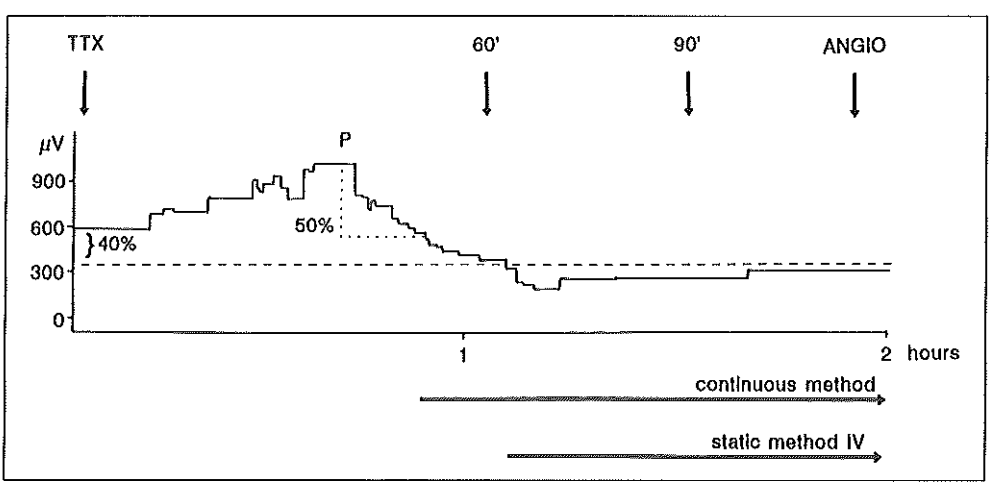

FIGURE 3. ST-segment deviation over time recorded in lead V_2 in a patient with a delayed peak (pattern 3). When the continuous method identified 50% ST recovery from a delayed peak (P) and assessed the infarct artery as patent, the static method predicted an occluded infarct-related artery, because of <40% ST recovery from the pretreatment electrocardiogram reference ST level *(dashed line)*. Further ST recovery progressed below the static method threshold 13 minutes later, leading to concordance in assessment from that moment onward. Thus, although the continuous method and static method IV disagree in patency assessment at 60 minutes after onset of thrombolytic therapy (TTX), they agree 90 minutes and at the moment of angiography almost 2 hours after onset of treatment. The 4 *vertical arrows* indicate timing of the following: onset of thrombolytic therapy (TTX), patency assessments performed at 60 minutes (60') and 90 minutes (90') after onset of treatment, and the moment of angiography (ANGIO). The 2 *horizontal arrows* indicate the time during which the continuous method or static method IV would assess the infarct-related artery as patent. Angiography revealed Thrombolysis in Myocardial Infarction trial grade 3 flow through a proximal left anterior descending artery lesion.

all pattern of ST recovery. Disagreement in patency assessment was more common earlier after thrombolytic therapy and was most often related to ongoing dynamic behavior in ST recovery (patterns 3, 4 or 5).

DISCUSSION

A method of continuously updated ST-segment recovery analysis was developed using identification of true maximal and minimal ST deviation as they occur to allow real-time noninvasive patency assessment of the infarct-related artery.[16–18] The added computational demands and need for a dedicated ST monitor must be weighed against simpler methods comparing static pre- and post-treatment electrocardiograms. These data suggest that static methods may undersample during dynamic periods early in acute myocardial infarction and therefore miss important additional information regarding ST recovery or reelevation. Relative concordance between the continuous method and 4 of the 5 static methods was seen when compared with simultaneous angiography a median of 2 hours after onset of thrombolytic treatment. Population size restricted detection of modest differences (type II error). Disagreements early after therapy were mainly seen after a delayed peak ST level (Figure 3). At least 5 patterns of ST recovery could be characterized, similar to descriptions by Dellborg et al.[20] One cannot predict in advance which pattern a patient will follow early after thrombolytic treatment. It is our supposition that often the timing of monitoring onset relative to the onset of infarction defines these patterns. When cyclic flow is present, varying onset of ST monitoring may result in pattern changes. Other reasons for these dynamic patterns could be the effect of collaterals,[23–26] or worsening of ischemia due to reperfusion injury.[27] Whereas these data do not further clarify underlying mechanisms, the frequency of these patterns is notable. In addition, precisely which patients may evidence which pattern, and when ST recovery or recurrent elevation are likely to occur are also highly unpredictable. Definition of the ST recovery pattern in individual patients requires frequent electrocardiographic sampling, which can be facilitated with an automated device.

Study limitations: Only 82 of the 144 TAMI 7 patients with analyzable ST-monitor recordings were selected for this study. Strict criteria were set to accommodate stipulations of all methods as closely as possible. Thus, the resultant population size was small. Subtle accuracy differences relative to angiography could therefore not be evaluated.

Although early infarct-related artery patency is a major determinant of survival,[1–10] characterization of physiologically adequate reperfusion or benefit of secondary reperfusion strategies remains controversial. This is particularly true in patients with TIMI grade 2 flow[28,29] or collateralized occlusion.[23–26] Earlier published reports stated that 8 of 10 patients with TIMI grade 2 flow and 4 of 10 patients with collateralized occlusion display ST recovery,[18] and could therefore be considered patent. Despite the controversial nature of the angiographic "gold standard" itself, all ST-recovery methods would be expected to be similarly affected.

Patients with prior Q-wave infarctions in the same area of ST elevation were not enrolled in the TAMI 7 trial. It is not known whether this may somewhat limit the generalization of the performance of these methods. It is expected that the continuous and static methods would be similarly affected.

Clinical implications of cyclic reperfusion are not yet fully understood, although preliminary evidence suggests that it has functional significance.[19,20] A single electrocardiogram only gives a "snap-shot" assessment and would miss this diagnosis by undersampling. Continuous ST monitoring can help define clinical relevance and response to treatment of such unstable infarct-related artery behavior.

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Chapter 10

Discussion

DISCUSSION

I: Intermittent coronary reperfusion

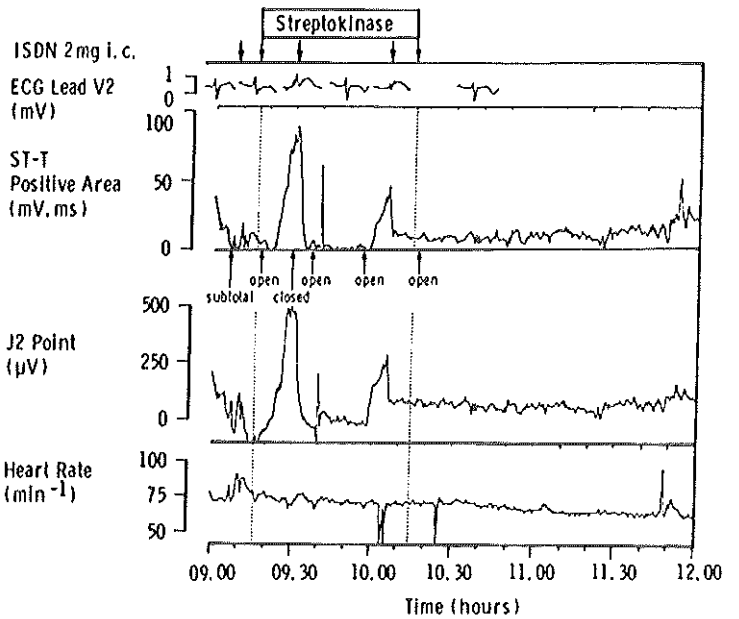
Hacket and co-workers demonstrated the close temporal relation between ST-segment elevation and coronary occlusion in 45 acute myocardial infarction patients prior to and following intracoronary infusion of streptokinase using continuous ST-segment Holter monitoring with concomitant serial angiographic observations.[1] Fifteen patients demonstrated 29 episodes of transient ST normalization, 12 (in 8 patients) occurred spontaneously prior to coronary angiography, and 17 (in 8 patients) during coronary catheterization of which 13 (in 7 patients) occurred during streptokinase infusion. Occlusion was always found during episodes of ST-segment elevation and patency coincided with resolution of ST-segment elevation (Figure 1). Coronary occlusion in the early phase of myocardial infarction was frequently intermittent and was reflected by ST-segment recovery and re-elevation. Table 1 lists the percentages of patients with ST evidence of intermittent reperfusion in 7 different studies.[1-7] While different therapies aimed at reperfusion were applied, intermittent reperfusion was observed consistently in approximately 37% of the patients (95% confidence interval 34 to 40%), of which 27% (19 to 36%) occurred before either thrombolytic therapy or coronary angioplasty was initiated. This may be explained by unstable plaques resulting in intermittent coronary occlusion, the dynamics of the thrombus formation and breakdown under influence of both treatment with vasodilators, aspirin, heparin, or thrombolytics, coronary spasm, or intermittent collateral blood supply.[1-4,8-10] It has been reported that patients with intermittent occlusion as evidenced by dynamic ST changes had a larger infarct size as recognized by higher maximum Lactate Dehydrogenase-1 level, a more pronounced change in QRS vector after 24 hours, a longer time to peak Creatine Kinase, and a (non-significant) tendency towards higher 1 year mortality than patients who do not show ST evidence of intermittent reperfusion.[4] Furthermore, it was noted that a beneficial effect of rt-PA could not be shown in enzymatic parameters of infarct size, electrocardiographic parameters of infarct limitation, or clinical outcome when compared with the placebo group in the patient group with ST evidence of intermittent reperfusion.[4] In 618 patients of the GUSTO-I ECG substudy a weak but significant inverse relationship was found between the presence of recurrent ST elevation and left ventricular ejection fraction ($r = -0.16$, $p = 0.001$).[7]

It is not known whether these unfavorable outcomes are caused by for instance repeated reperfusion injury, longer total occlusion duration, or higher incidence in more proximal coronary lesions, or whether this is largely due to the fact that intermittent reperfusion is more obvious when infarction generates higher ST-segment amplitudes. Although more studies into the pathophysiology and clinical relevance of intermittent reperfusion are needed, these data strongly suggest that cyclic reperfusion might have clinical significance regarding outcome and effect of treatment. Whether there is a difference in mechanism and outcome between early versus late recurrent occlusion may also need further investigation.

II: Accuracy of continuously updated ST-segment recovery analysis

The most reliable method to assess coro-

Figure 1



Computerized analysis of a continuous ambulatory electrocardiogram (Holter - ECG) from a patient with recurrent ST-segment elevation and coronary reocclusion during continuous Streptokinase infusion. Initially, ST-segment elevation was recorded at 9:06 hours, and after intra-coronary isosorbide dinitrate (ISDN), the ST-segment returned to baseline. ST-segment elevation recurred with angiographically documented coronary occlusion at 9:30 hours during continuous Streptokinase infusion. After additional ISDN, the ST-segment again returned to baseline with angiographic documentation of coronary recanalization. ST-segment elevation recurred at 9:58 hours, but coronary angiography was not performed during this episode. After additional ISDN the ST-segment again returned to baseline. *Reprinted by permission of The New England Journal of Medicine, Hacket D, Davies G, Chierchia S, Maseri A; volume 317: pp 1055-9, 1987. Copyright 1987. Massachusetts Medical Society. All rights reserved.*

nary reperfusion status is repeated coronary angiography. This, however, is a burden on the patient and hospital resources, while catheterization laboratory facilities are not available to all hospitals. A reliable, noninvasive assessment technique able to detect reperfusion and recurrent occlusion over time would therefore be useful. As indicated above, ST changes correlate with angiographic patency. However, it should be appreciated that static patency assessments comparing a single post-treatment ECG with a pre-treatment ECG will misrepresent the physiologic behavior of reperfusion when one or multiple recurrent occlusions occur or when ST recovery occurs following a late peak in ST elevation.[6, 11, 12] For this reason continuously updated ST-segment recovery analysis has been developed. Table 2 lists performance parameters of 4 studies using continuously updated ST-segment recovery analysis to predict simultaneous angiographic coronary flow status of the infarct related artery.[3,13-15] Continuously updated ST-segment recovery analysis has

Table 1

Author	N	treatment	A/ST	intermittent reperfusion		before treatment	
Davies[2]	9	IC-SK	A+ST	6	(67%)	1	(11%)
Hackett[1]	45	IC-SK	A+ST	22	(49%)	8	(21%)
Krucoff[3]	22	IV-TTX PTCA	A+ST	11	(50%)	5	(31%)
Dellborg[4]	103	rt-PA Placebo	ST	35	(34%)	16	(34%) *
Kwon[5]	31	IV-TTX	ST	11	35%)	not reported	
Veldkamp[6]	82	IV-TTX	ST	32	(39%)	not reported	
Langer[7]	618	IV-TTX	ST	221	(36%)	not reported	
	910			338	(37%)	30/110	(27%)

Occurrence of intermittent reperfusion in acute myocardial infarction as reported in 7 different studies.[1-7] N = the number of patients in the study; A = serial angiographic observations; ST = continuous electrocardiographic ST-segment monitoring; IC-SK = intracoronary streptokinase; IV-TTX = intra-venous thrombolytic treatment; rt-PA = recombinant tissue type plasminogen activator; * in the placebo group.

shown to be a useful noninvasive indicator, although especially the sensitivity for occlusion may be improved. Use of continuously updated ST-segment recovery analysis has not yet been validated in patients with delayed ventricular conduction, but this comprises only a small part of the population of acute myocardial infarction patients.[13, 16, 17] More restricting is the requirement that initial ST deviation indicating coronary occlusion is still present when ST monitoring is initiated. In fact, accuracy of patency assessment by continuous ST-segment recovery analysis strongly depends on peak ST deviation.[15,18] This requirement favors the analysis of anterior above inferior infarctions and both above posterior infarctions.[19, 20] Availability of hard-copy electrocardiograms recorded during coronary occlusion can substitute missing data prior to initiation of ST-segment monitoring, but this limits the detection of the onset and stability of reperfusion.

III: ST MONITORING FOR TRIAGE FOLLOWING THROMBOLYTIC TREATMENT

To avoid unnecessary bleeding risk, thrombolytic therapy might be discontinued in acute myocardial infarction patients when ST recovery evidences early

Table 2

Author	N	TIMI 0-1	Sens.	Spec.	Acc.	PPV	NPV	Comments
Krucoff[3]	44	-	90%	92%	-	-	-	pilot study; formal algorithm, 44 serial observations in 22 pts.; not blinded; few data on performance
Krucoff[13]	144	39 (27%)	64%	90%	83%	71%	87%	correct study design; formal algorithm
Dellborg[14]	96	26 (27%)	73%	83%	80%	61%	89%	correct study design; both ST nd QRS information used; only partially formalized algorithm
Klootwijk[15]	302	105 (35%)	44%	84%	70%	59%	74%	complex study design; formal simple algorithm; late onset of monitoring; relatively inexperienced participants

Four studies reporting the performance of continuously updated ST-segment recovery analysis as compared against simultaneous coronary angiography.[3,13-15] N = number of observations; TIMI 0-1 = thrombolysis in myocardial infarction flow grade 0 or 1 All studies considered TIMI flow grade 2 or 3 to reflect infarct related artery patency, presence or absence of collateral blood supply was not taken into account; Sens. = sensitivity, the ability to detect an angiographically occluded infarct related artery; Spec. = specificity, the ability to correctly predict an angiographically open infarct related artery; Acc. = accuracy, the percentage of correct predictions overall; PPV = positive predictive value, the percentage of correct predictions of an occluded infarct related artery; NPV = negative predictive value, the percentage of correct predictions of a patent infarct related artery; - = information was not reported or reconstructible from given data.

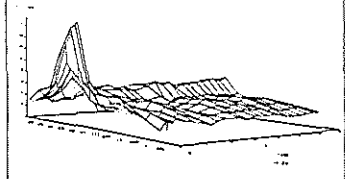
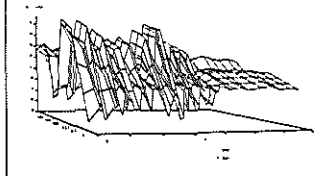
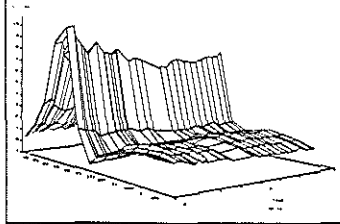
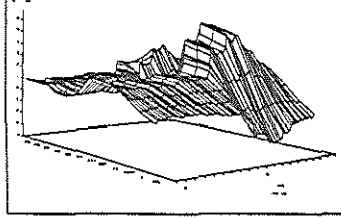
Figure 2
Possible treatment options (right column) that could be chosen depending on the reperfusion behavior following thrombolytic therapy for acute myocardial infarction as evidenced by continuously updated 12-lead ST-segment recovery analysis (2 columns on the left side). In the 3 dimensional graphs in the far left column the X-axis represents each of the 12 leads, the Y-axis represents the ST deviation measured 60 milliseconds after J-point, and the Z-axis represents time.[3] The third column explains clinical implications of the different types of reperfusion behavior. Early stable reperfusion is associated with limitation of infarct size, electrical stability of the myocardium, and improved survival.[42-49] Early cyclic reperfusion is associated with large infarct size and decreased survival.[4,7] No reperfusion is related with larger infarcts, electrical instability, and decreased survival.[42-51] Recurrent occlusion, potentially resulting in recurrent infarction is associated with increased morbidity and mortality.[52,53]

It has been suggested that thrombolytic therapy may be stopped once ST recovery signifying reperfusion has occurred.[21,22] When ST recovery is followed by recurrent ST elevation suggesting cyclic reperfusion, addition of anti-coagulants, platelet inhibitors, or higher doses of vasodilators may be helpful in stabilizing reperfusion.[1,23-33] When no reperfusion occurs following thrombolytic therapy, or when late recurrent occlusion occurs, rescue thrombolytic therapy,[34-37] or angiography with rescue PTCA[38-40] or intra-coronary thrombolytic therapy[41] may be considered. Trials testing these strategies following triage with continuously updated ST-segment recovery analysis and other noninvasive patency assessments are warranted.

reperfusion of the infarct related artery.[21,22] Patients suffering from acute myocardial infarction, in whom thrombolytic therapy fails to provide early and stable reperfusion might benefit from additional treatment such as rescue angioplasty, rescue thrombolysis, or from additional medical treatment such as antithrombin or anti-platelet compounds.[23-41] Figure 2 illustrates the possible treatment options that could be chosen depending on the reperfusion behavior as evidenced by continuously updated ST-segment recovery analysis. Many of these options are under debate or have not yet been investigated, partly because a useful (continuous) non-invasive patency assessment method was not available until the development of continuous real-time ECG analysis. The potential value of stopping thrombolytic treatment once reperfusion has been achieved, rescue thrombolytic therapy, and rescue coronary angioplasty (PTCA) will be discussed below. Further research into the reperfusion patterns following thrombolytic therapy and treatment strategies dependent on the specific reperfusion pattern is required, so that treatment regimens can be optimized according to the individual's response.

Stopping thrombolytic treatment once reperfusion has been achieved

When rapid ST-segment recovery indicates reperfusion through the infarct related artery administration of the thrombolytic agent might be discontinued to reduce the risk of intracranial hemorrhage.[22] Further-therapy should be aimed at preventing recurrent occlusion. One might consider that continuation of thrombolytic drug administration beyond the moment of reperfusion could help to resolve the remaining thrombus. However, little if any benefit of prolonged administration of rt-PA was observed in a trial addressing this issue,[54,55] while prolonged administration of thrombolytics might increase the risk of bleeding complications.[56] It should there-fore be investigated whether cessation of thrombolytic therapy with subsequent anti-platelet or anti-coagulant therapy once ST evidence of reperfusion occurs does indeed reduce bleeding complica-tions without compromising stability of reperfusion.

ST pattern	suggesting	clinical	suggested action
	**early stable reperfusion**	small infarct size electrical stability **survival ↑**	stop thrombolytic therapy
	**early cyclic reperfusion**	large infarct size **survival ↓**	stop thrombolytic therapy anti-coagulants platelet inhibitors vasodilators ↑
	**no reperfusion**	large infarct size electrical instability **survival ↓↓**	repeat thrombolytic therapy urgent angiography & PTCA
	**late recurrent occlusion**	recurrent infarction **survival ↓↓**	repeat thrombolytic therapy urgent angiography & PTCA

Rescue thrombolytic therapy

In patients with persistence of ST elevation, indicating failure of thrombolytic therapy, or with recurrent ST elevation following initial signs of successful reperfusion, addition of a second thrombolytic agent or prolonged infusion of the same drug might be successful ("rescue thrombolysis"). So far the efficacy and safety of a second dose of thrombolytic therapy for recurrent occlusion following initial thrombolytic therapy has been addressed in a limited number of patients in 4 reports (Table 3).[34-37] These studies suggest high short term efficacy with a modest increase in bleeding complications following retreatment with either recombinant tissue-type plasminogen activator (alteplase) or streptokinase. Repeat administration of streptokinase may be accompanied by allergic reactions, and neutralizing antibodies sufficient to inhibit conventional doses of streptokinase may develop as early as 4 days after the initial administration.[35] Repeated administration of streptokinase or streptokinase containing anistreplase (APSAC) should therefore be avoided. The small groups preclude definite conclusions and in neither of these studies a comparison was made with other strategies or placebo. It is therefore not known whether recurrent ischemia would have resolved spontaneously in these patients. Still, in all 4 studies recurrent ischemia of ≥ 30 minutes was required, suggesting that an intervention was warranted. Further studies are needed on both safety and efficacy, comparing them with either placebo or other strategies such as rescue PTCA. The value of a prolonged dose of the same agent or a second dose of a different agent when the primary thrombolytic agent was unsuccessful remains to be investigated. Most importantly, studies are needed focussing on the prevention of recurrent occlusion.

Rescue coronary angioplasty

Coronary angiography with "rescue PTCA" in patients with ongoing or recurrent occlusion has been under debate for about a decade now but only 2 randomized trials have been organized.[38,39] The strong polarization between proponents and opponents, the deficiency of 24 hour catheterization facilities, and the lack of reliable non-invasive patency assessment methods have made it difficult to organize a large enough multi-center trial that can give a definite answer.[40] Table 4 lists arguments in favor and against a strategy of rescue PTCA.

Belenkie and co-workers randomized 28 patients with an angiographically determined failure of thrombolytic therapy.[38] Of the 16 patients treated with rescue angioplasty only 1 patient died during hospitalization, notably 1 of the 3 patients in whom PTCA failed to restore patency. Of the 12 conservatively treated patients 4 died ($p = 0.13$, NS). Ellis and co-workers randomized 151 anterior myocardial infarction patients with an angiographically occluded infarct related artery following thrombolytic therapy to rescue PTCA ($n = 78$) or a conservative strategy ($n = 73$) 1.5 to 8 hrs following onset of symptoms.[39] The prespecified primary endpoint of resting ejection fraction after 30 days did not show any improvement following rescue PTCA: 40 ± 11% after rescue PTCA versus 39 ± 12% following the conservative strategy. Secondary endpoints were 30 day mortality or congestive heart failure (class III-IV) at 30 days. A trend toward clinical improvement following rescue PTCA was noted: death in 5% and 10% ($p = 0.18$); congestive heart failure in 1% and 7% ($p = 0.11$); and death or congestive heart failure in 6% and 17% ($p = 0.05$) following rescue PTCA versus conservative treatment respectively. Furthermore, exercise ejection fraction did show significant improvement

following rescue PTCA: 43 ± 15% following rescue PTCA versus 38 ± 13% following conservative treatment ($p = 0.04$).

No definitive answers regarding the value of rescue PTCA can be given based on current evidence. With the data available a conservative strategy seems warranted. Rescue PTCA should be reserved for patients in whom the clinical, hemodynamic status deteriorates following standard conservative treatment. A sufficiently large randomized trial of rescue PTCA versus conservative treatment with noninvasive ST monitoring and or biochemical patency assessment for the primary triage seems warranted. Furthermore, comparison with rescue thrombolytic therapy should be made if efficacy and safety of that strategy have been established.

IV: ST MONITORING IN CLINICAL TRIALS

Mortality following acute myocardial infarction occurs relatively infrequent and studies with a mortality endpoint therefore require large study populations. Infarct size, left ventricular function, and angiographic patency of the infarct related artery have therefore been used as alternative endpoints. Since angiography is not available in every hospital there is an increased interest in simple noninvasive patency assessments.[57,58] Early opening of the infarct related artery is directly related to limitation of infarct size, preservation of left ventricular function, and a better clinical outcome.[42-51] Previous studies have shown the unfavorable results of recurrent occlusion.[4,7,52,53] The documentation and timing of reperfusion and the assessment of re-occlusion with continuously updated ST-segment recovery analysis might therefore serve as important endpoints in trials comparing drug regimens aimed at early stable reperfusion.

The GUSTO-1 ST-segment monitoring substudy was the first large scale attempt to compare speed and stability of reperfusion as assessed with continuously updated ST-segment recovery analysis in 4 different thrombolytic regimens: 1) streptokinase with subcutaneous heparin; 2) streptokinase with intravenous heparin; 3) accelerated rt-PA with intravenous heparin; and 4) streptokinase and rt-PA with intravenous heparin.[7,59] In this study 3 different devices were used: continuous vector electrocardiography, continuous 12-lead monitoring, and 3 channel Holter recording.[60] In contrast with the angiographic substudy in which the accelerated rt-PA regimen showed higher early patency rates,[46] no significant difference was found in time to first 50% ST recovery. The ability to detect differences in time to 50% ST recovery in this study may have been hampered by the uncontrolled and variable time to initiation of ST-segment monitoring and by differences among devices, such as algorithms used for detection and evaluation of ST shift.[60] These concerns are supported by a multiple regression model in which time to onset of ST monitoring was the most significant predictor of time to 50% recovery, followed closely by the type of device used. Furthermore, technical requirements such as onset of monitoring within 1 hour following initiation of thrombolytic therapy, no interruption of monitoring prior to 50% ST recovery, or a peak amplitude ≥ 200 μV where not met in over 40% of the patients who underwent ST monitoring. The greater than expected number of patients excluded from analysis has reduced the power to detect differences.

The second a priori assumption in the GUSTO-1 ST-segment monitoring substudy was that patients treated with streptokinase would show greater stability of ST recovery.[7] The results showed that ST-segment re-elevation reflecting recurrent

Table 3

author	Barbash[34]	White[35]	Simoons[36]	Mendia[37]
N	52	31	26	11
N control group	1447		618	
initial TTX	rt-PA 100-120 mg or SK 1.5 million U	SK 1.5 million U or rt-PA 100 mg	rt-PA 100 mg	rt-PA 100 mg
2nd TTX	rt-PA 100-120 mg	SK 1.5 million U or rt-PA 100 mg	rt-PA 50 mg (< 24 hrs) rt-PA 100 mg (> 24 hrs)	rt-PA 100 mg or SK 1.5 million U
time to 2nd TTX	≤ 1 hr (-8 days)	5 days (1-716)	≤ 5 hrs (-77)	10.5 days (1-28)
ST↓ after 2nd TTX	44 (85%)	-	26 (100%)	11 (100%)
angio-patency after 2nd TTX	18/29 (62%) *	16/22 (73%)**	14/26 (54%) ***	10/10 (100%)****
bleeding compl. after 2nd TTX	19%	13%	23%	-
bleeding compl. in control group	6%		19%	
transfusion after 2nd TTX	4%	3%	12%	-
transfusion in control group	-		3%	
ICH after 2nd TTX	0	1	0	-
ICH in control group	-		2	

Table 3: Efficacy and safety of repeated administration of recombinant tissue-type plasminogen activator as reported in 4 studies.[34-37] In the first study patients received either intravenous heparin, subcutaneous heparin, or placebo, depending on the main trial in which they where enrolled. In the second study 19 patients received intravenous heparin. In the third study patients were randomized between intravenous heparin or placebo. Patients in the fourth study were treated with subcutaneous or intravenous heparin. All patients received aspirin, and 12 patients in the second study also received dipyridamole 400 mg daily. The control groups in the first and third study consisted of patients not selected for repeat administration of thrombolytic therapy. TTX = thrombolytic treatment; rt-PA = recombinant tissue-type plasminogen activator; SK = streptokinase; time to 2nd dose of thrombolytic therapy is reported as median and (one sided) range; ST↓ = ST recovery following elevation, signifying reperfusion following the recurrent occlusion; angio-patency = angiographically documented patency following recurrent occlusion; 1st TTX = the initial thrombolytic treatment; 2nd TTX = retreatment with recombinant tissue-type plasminogen activator; ICH = number of patients with intracranial hemorrhage; - = not reported.

* Angiography was performed only when a second recurrent occlusion was suspected due to recurrent chest pain and ST elevation.

** Twenty-two patients underwent late angiography. Reasons not to perform late angiography were early dead in 3, emergency CABG in 1, and known coronary anatomy due to early angiography in 5.

*** Angiography was performed a median of 64 hours following the second dose of alteplase (range 2 to 120 hours).

**** Angiography was performed ≥ 72 hours after the acute ischemic symptoms.

Table 4

PRO rescue PTCA	CONTRA rescue PTCA
1. increased early infarct related artery patency rates	1. no proven benefit due to lack of randomized trials
2. patency, early or late, is associated with improved short and long term survival	2. spontaneous late reperfusion may occur (catch-up patency)
3. relatively late reperfusion may lead to improved infarct healing, increased electrical stability	3. complications related to emergency angiography and PTCA may outbalance benefits
4. late reperfusion may provide a source for collateral flow in multi-vessel disease	4. recurrent occlusion following PTCA may reduce the salutary effect of a patent infarct related artery
	5. may require referral to specialized centers
	6. involves costly, impractical procedures

Arguments pro and contra rescue angioplasty (PTCA) for failed or recurrent occlusion of the infarct related artery following thrombolytic treatment.

occlusion occurred equally in each treatment group. This finding does support the similar re-infarction and re-occlusion rates seen in the main trial and the angiographic substudy.[46,59] Results regarding time to first 50% recovery and stability of ST recovery for the 4 treatment arms were independent of the device used.

V: ST MONITORING TO DETERMINE PROGNOSIS

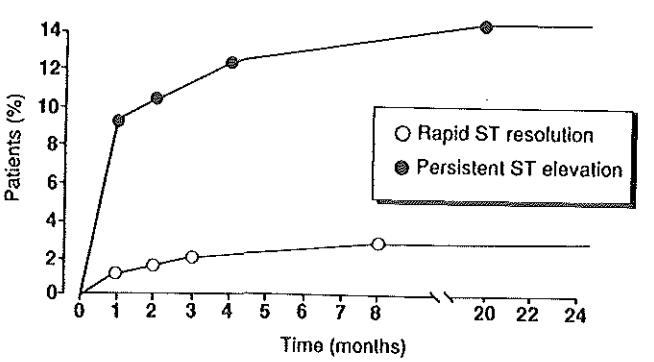
Besides the possibility to tailor thrombolytic and adjuvant therapy to the patient's individual response, continuous real-time ST-segment monitoring might be helpful in determining the prognosis of individual patients. Barbash and co-workers showed in a series of 286 patients that a reduction in the summated ST elevation of ≥ 50% from the admission ECG 1 hour after treatment onset with alteplase (rt-PA) was associated with a significantly smaller infarct size (release of creatine kinase), better preservation of left ventricular function, lower morbidity, and improved short and long term survival (Table 5/ Figure 3).[61] It is noteworthy that the summated ST elevation at admission had no independent predictive value for clinical outcome when presence or absence of ST recovery was taken into account. The association between ST recovery and outcome was less pronounced in patients with inferior infarction as compared with patients with anterior infarction as the former already had a smaller enzymatic infarct size, with a better clinical outcome

Table 5

rapid ST recovery	YES (n = 189)	NO (n = 97)	
24 hrs. total CK release	5248 IU (SD 4265)	10553 IU (SD 7762)	p < 0.0001
discharge LVEF	55% (SD 12)	44% (SD 14)	p < 0.0001
60-day mortality	3 (1.6%)	10 (10.3%)	p = 0.0015
CHF	8 (4.2%)	18 (18.6%)	p < 0.001

The effect of rapid ST-segment recovery following treatment with rt-PA (≥ 50% reduction in summated ST deviation within 1 hour following treatment onset) on: 1) total Creatine Kinase (CK) release in 24 hours as an area under the curve of several samples; 2) left ventricular ejection fraction (LVEF) prior to discharge assessed with radionuclide gated blood pool scan; 3) 60 day mortality; and 4) presence of congestive heart failure (CHF) during hospitalization (CHF at admission excluded patients for this study). SD = standard deviation. *Data reported by Barbash et al.*.[61]

Figure 3



Cumulative mortality (%) of patients with rapid resolution of ST elevation and without. *Reprinted by permission of the British Heart Journal, Barbash GI, Roth A, Hod H, Miller HI, Rath S, Har-Zavah Y, Modan M, Seligsohn U, Battler A, Kaplinsky E, Rabinowitz B, Laniado S; volume 64: pp 241-7, 1990. Copyright 1990. All rights reserved.*

and ejection fraction. Other factors that influenced left ventricular function were a history of prior infarction, presence of 3 vessel disease, age, and sex, while only a history of prior infarction was also a predictor of mortality. Saran and co-workers also found that rapid ST recovery was associated with preservation of left ventricular function.[62]

Preliminary data showed that patients without ST re-elevation indicating recurrent occlusion > 3 hours after onset of thrombolytic therapy have a lower morbidity and mortality than patients with unstable or failed reperfusion after 3 hours.[63] Prognostic importance of parameters derived from continuous monitoring such as presence and timing of rapid ST recovery, maximum amplitude and extent of the infarct zone, time to reperfusion and early or late stability of reperfusion need to be explored in large patient groups and should be compared and combined with other noninvasive clinical information (e.g. age, history of angina, history of prior infarction, enzymatic infarct size, left ventricular function, treatment delay, reperfusion therapy given, presence of congestive heart failure, electrocardiographic or enzymatic infarct size)[51,64] such that risk stratification and thus medical care following reperfusion therapy can be individualized as well. Ideally the duration of hospital stay can be shortened or lengthened based on individual risk assessments. A very low risk of complications could for instance lead to a shorter stay at the coronary care unit, followed by an earlier discharge.[65,66] On the other hand, high risk patients would require longer observation in the coronary care unit. Models predicting long term prognosis could also include outcomes of early ambulatory ST monitoring following discharge from the coronary care unit[67,68] or exercise treadmill electrocardiography prior or following hospital discharge.[69-71]

VI: Continuous ST monitoring devices

Arrhythmia monitoring systems

Electrocardiographic monitoring systems used to detect cardiac arrhythmias in real time are available in most coronary care units, intensive care units, medium care or step down units (telemetry), emergency rooms, catheterization laboratories, and surgical suites. However, many of these devices are not suitable for ST-monitoring, although the displayed electrocardio-graphic signal may show ST abnormalities. Often distortions of the low frequency content of the signal due to inadequate filtering techniques and 'baseline wander correction' may result in misleading morphologies of the ST-segment.[72] Furthermore, in most systems only one lead is displayed on the central monitoring station although many systems currently record 2 or 3 leads simultaneously. Lead orientation is focussed on arrhythmia detection rather than ischemia detection which results in decreased sensitivity for ST episodes occurring in other areas than the lead monitored.[73-75] Also, fatigue of the medical staff, partly due to the display of multiple patient tracings simultaneously results in under-reporting of ST-episodes.[76] Thus, these systems can only be used reliably for ST monitoring if: 1) filtering techniques result in an adequate low frequency response; 2) lead orientation allows detection of both ischemia and arrhythmias; and 3) proper ischemia detection algorithms are integrated, including storage of complexes and measurements for comparison in full disclosure format and trending of the ST deviation over time.

Holter recorders

The major disadvantage of Holter recorders applied in continuous ST monitoring

is the retrospective off-line analysis not allowing real-time triage at the bedside. Holter ST monitoring should therefore be restricted to use in comparative trials and research.[12,77] Furthermore, the number of leads monitored is restricted. A 3 lead system with a (pseudo-) orthogonal orientation such as an anterior lead V2, apical lead V5, and an inferior lead aVF or III should be preferred so that sufficient injury current is recorded for ST-segment recovery analysis.[72,74,75,78,79] It is also important to realize that ST-segment amplitudes measured on the bipolar Holter recordings are not fully comparable with ones measured on the unipolar precordial leads of the 12-lead ECG.[80] An advantage of Holter ST monitoring is that it records all beats without front-end selection or classification, making it appropriate for the parallel analysis of ST-segment recovery and arrhythmias in full disclosure.[81,82] Furthermore, many clinics already have Holter-recorders for the purpose of arrhythmia monitoring, and often their system is also suitable for ST-segment monitoring with an adequate frequency response and with an adequate analysis system. Familiarity with the device and financial considerations will lower the threshold for these hospitals to participate in multi-center trials.

Computer aided continuous multilead electrocardiography

Computer aided continuous multilead electrocardiographic devices were developed to provide real-time information on the dynamic ECG changes at the bedside with optional alarms warning the clinician when such changes occur. Two different approaches for real-time computer aided ECG monitoring have specifically been developed for ST-segment monitoring and are commercially available. The first one is based on the continuous sampling and averaging of the 12-lead ECG. This thesis describes parts of the development and application of one of these devices, known as the ST100, developed in close cooperation with and marketed by Mortara Instrument (Milwaukee, WI, USA). Other manufacturers have developed continuous multi-lead monitoring units based on conventional electrocardiographic leads as well.[83]

The second approach to real-time computer aided ECG monitoring is the continuous monitoring of the vector electrocardiogram, developed by Hodges, Sederholm, Grötum, Dellborg and co-workers.[84,85] This device, known as the MIDA 1000 was developed in close cooperation with and marketed by Ortivus Medical AB, Täby, Sweden. The 3 orthogonal vectorcardiographic leads X, Y and Z are computed from the Frank lead system and averaged to form mean vectorcardiographic complexes. In acute myocardial infarction studies the 2 most closely studied derived parameters are the QRS vector difference and the ST-vector magnitude. The QRS vector difference is especially sensitive to changes in the QRS morphology and duration, making it a parameter reflecting infarct evolution and conduction changes. The ST vector magnitude is the result of the ST-segment deflection in the 3 orthogonal leads and thereby reflects the presence or absence of ST deviation as a result of ischemia, similar to the recording of the ST deviation in the 12-lead device. Dellborg and co-workers reported on the performance of evaluation of the QRS vector difference and ST vector magnitude changes for noninvasive patency assessment (Table 2).[14] Only a marginal benefit from monitoring the QRS vector changes in addition to ST changes was found, namely for patients with only minor changes in the ST trend. So far no fully quantitative patency assessment algorithm

allowing real-time analysis has been developed using continuous vectorcardiographic parameters. Thus, for bedside triage one has to rely on visual inspection of the trendlines of these 2 parameters over time. The vectorcardiographic format is only understood well by skilled medical personnel, although others generally intuitively will recognize parallels with the standard 12-lead ECG. Its major advantage is that spatial parameters of ST recovery are easy to represent in a single parameter.

VII: Other Noninvasive Patency Assessment Methods

Arrhythmia monitoring

It has been noted as early as in 1935 that arrhythmias may accompany occlusion and reperfusion of coronary arteries.[86] Accelerated idioventricular rhythm (AIVR) occurs most frequently during reperfusion.[87] early occurring AIVR seems to be the most reliable of the "reperfusion arrhythmias".[87-92] Table 6 lists 6 studies focussing on the performance of early AIVR as a predictor of infarct related artery patency. With current knowledge it can be considered a limitation of these studies that presence of AIVR was not correlated with other continuous simultaneous registration of reperfusion behavior such as multiple angiograms at the moment of arrhythmia or continuous multilead ST-segment recovery analysis.[81,82] The possibility of a transient reperfusion causing the arrhythmia could have been missed in the patient groups labeled occluded by a single angiographic assessment. Reported sensitivity and specificity varied widely per study. No clear relation was observed between the type of reperfusion therapy (intravenous versus intracoronary) or the administration of intravenous lidocaine and the performance of AIVR as a patency predictor. As can be seen in Figure 4, sensitivity and specificity strongly related to the reported incidence of AIVR, which in itself varied widely per study (5% to 71%). Incidence of AIVR clearly depended on the monitoring duration following onset of thrombolytic therapy: the shorter the monitoring time, the lower the incidence and thus the lower the sensitivity and the higher the specificity for reperfusion. Differences in incidence may also be explained by differences in AIVR definition, while other potential causes could not be reconstructed from reported data. Combined analysis of these studies as shown in Table 7 support the assumption that especially AIVR early following thrombolytic therapy might herald reperfusion with high specificity but with low sensitivity due to its infrequent incidence of 35%. The negative predictive value of 43% indicates that AIVR cannot be used as a single noninvasive marker of infarct related artery patency. Furthermore, a direct temporal relationship between ST recovery as a marker of reperfusion and the occurrence of reperfusion arrhythmias was not found in one study.[81]

Biochemical assays

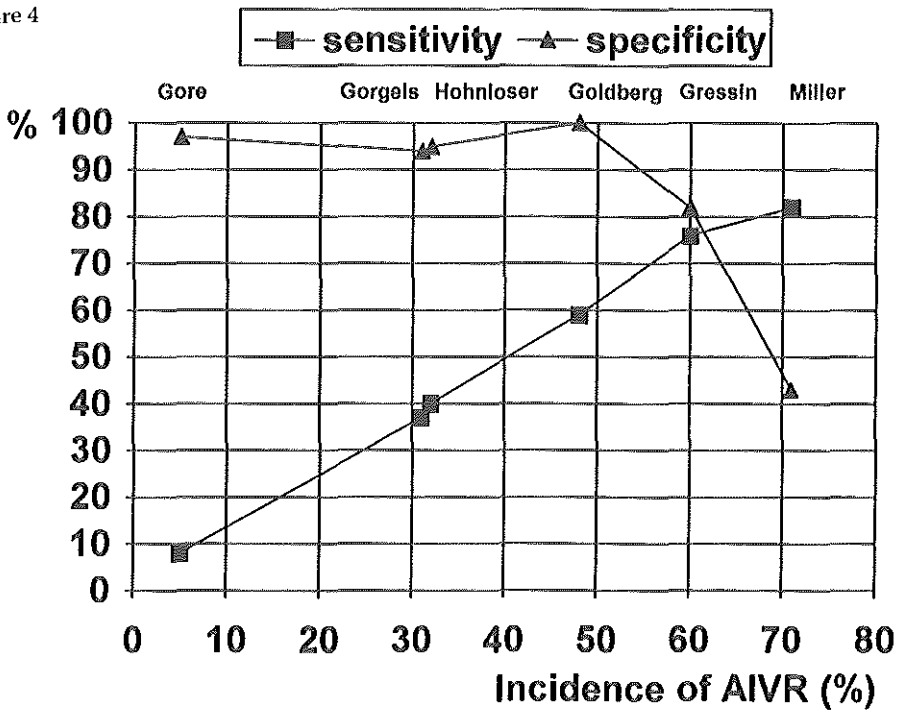
Presence or absence of infarct related artery reperfusion can be detected by rapid assays of myocardial proteins in plasma, such as the enzyme Creatine Kinase (CK),[91,93-96] the cardiospecific isoform CK-MB,[94-100] myoglobin,[94-96,98] and the cardiac specific antigen Troponin T.[95,101] An early rise in plasma levels of any of these proteins indicates reperfusion. When reperfusion occurs, the rate of release of these substances abruptly increases, probably as a consequence of the increase of blood flow through the necrotic area ("wash-out phenomenon"). Acceleration in breakdown of compromised myocytic membranes at the moment of reperfusion

Table 6

author	N	ttx	TIMI 2-3	Sens.	Spec.	Incid.	Lidocaine	monitoring duration	comments
Goldberg[87]	21	IC	81%	59%	100%	48%	all	during ttx	definitoion of AIVR nor reported
Miller[88]	31	IC	55%	82%	43%	71%	all	12 hours	
Gorgels[89]	87	IC IV	80%	37%	94%	31%	49% on demand	during ttx	observation duration not reported
Gore[90]	56	IC	45%	8%	97%	5%	all	90 min.	definiton of AIVR not reported
Hohnloser[91]	82	IV	77%	40%	95%	32%	not reported	90 min.	
Gressin[92]	40	IV	73%	76%	82%	60%	32% on demand	6 hours	

Reported performance of early AIVR (accelerated idioventricular rhythm) as a predictor of infarct related artery patency in 6 studies.[87-92] N = the population size; ttx = the type of thrombolytic therapy involved; TIMI 2-3 = the percentage of patients with a reperfused infarct related artery at coronary angiography; Sens. = sensitivity, the ability to detect an angiographically reperfused infarct related artery; Spec. = specificity, the ability to correctly predict an angiographically occluded infarct related artery; Incid. = the incidence of AIVR; Lidocaine = the percentage of patients receiving intravenous lidocaine; IC = intra-coronary thrombolytic therapy; IV = intravenous thrombolytic therapy; VT = ventricular tachycardia.

Figure 4



Reported sensitivity and specificity of early AIVR (accelerated idioventricular rhythm) as a predictor of infarct related artery patency related to the incidence of AIVR in 6 studies.[87-92]

Table 7

Combined analysis of AIVR (N = 317)	
pre-test probability of patency	70%
incidence of AIVR	35%
sensitivity	45%
specificity	97%
positive predictive value	97%
negative predictive value	43%
accuracy	61%

The combined analysis using the results of 6 studies assessing performance of occurrence of early AIVR as a noninvasive predictor of infarct related artery patency.[87-92] See also Table 6.

may also contribute to the increased release ("reperfusion injury"). The increased early release following reperfusion can be distinguished from failed reperfusion by an earlier peak plasma level and/or a higher rate of appearance into the bloodstream.

The ratio of the Creatine Kinase (CK) subforms CK-MB2/CK-MB1 may also be used for noninvasive patency assessment.[102] Following reperfusion the unmodified subform MB2 is released into the bloodstream at an increased rate. Enzymatic conversion into the MB1 subform occurs in the blood. With the sudden increase of MB2 typical of reperfused infarction, the accumulation of MB2 in plasma exceeds the conversion to MB1, resulting in an increased MB2/MB1 ratio. In contrast, nonreperfused infarction is characterized by a more gradual release of MB2 with a relative constant conversion into MB1, resulting in a lower MB2/MB1 ratio.

Patency assessments based on differences in the rate of appearance in plasma between patients with and without reperfusion should be preferred above determination of the time from treatment to peak plasma levels, since waiting for the peaks to occur with serial plasma determinations delays the clinical triage.[12,95] Simple assays that can be performed 24 hours a day preferably by the coronary care unit personnel, with rapid results, are essential for clinical utility.[12,95] Table 8 lists published assays that have been tested in humans and can be used in the early assessment of infarct related artery patency.[95,97,98,102] All assessment methods seem to have adequate sensitivity and specificity. Except for the Troponin-T and CK MB2/MB1 ratio based assessments, all assays can be performed relatively easily and quickly with current techniques and can therefore be used for early triage. More simplified and more rapid tests are awaited. It should be appreciated however that myoglobin and CK are non-cardiospecific proteins, giving (false positive) increased levels following muscle trauma, resuscitation, renal impairment, vigorous exercise and other conditions. Serial enzyme assays may indicate the presence of cyclic reperfusion, as is demonstrated in Figure 5.[12] Recurrent occlusion will only be detected when subsequent reperfusion results in a second rise of released enzymes, or when the first rise in the enzyme curve is aborted suddenly. Application of serial enzyme assays for dynamic patency monitoring requires further development.

Comparing and combining ST monitoring, arrhythmia monitoring, and biochemical assays

Continuously updated ST-segment recovery analysis has the advantage of detecting both (failure of) reperfusion and recurrent occlusion. Biochemical assays currently provide a static assessment only. No distinction is made between stable versus unstable reperfusion and detection of recurrent occlusions depends on other assessments. Arrhythmia monitoring is not useful as a single indicator of reperfusion due to the infrequent occurrence of AIVR. Furthermore, it does not indicate recurrent occlusion.

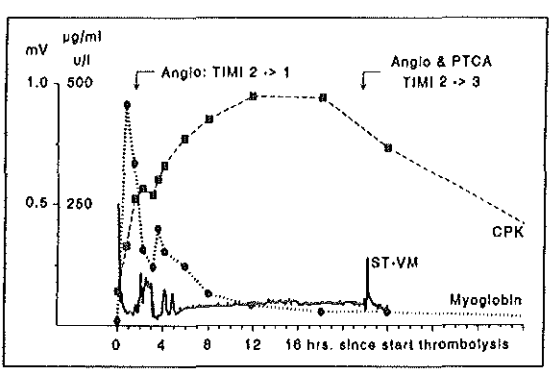
As discussed previously there are two situations in which ST-monitoring is not applicable. Firstly, it has not yet been validated in patients with delayed ventricular conduction, but that comprises a small part of the population of acute myocardial infarction patients.[13,16,17] More restricting is the requirement that initial ST deviation reflective of coronary occlusion should be present when ST monitoring is initiated. Accuracy of patency assessment by continuous ST-segment recovery analysis strongly depends on monitored peak ST deviation.[15,18] When ST monitoring is

Table 8

assay	N	time	Sens.	Spec.	test
CK					20 min.
Zabel[95]	63	90 min.	87%	71%	
CK-MB					15 min.
Garabedian[97]	29	90 min.	83%	100%	
Ellis[98]	42	120 min.	85%	100%	
Zabel[95]	63	90 min.	85%	71%	
CK MB2/MB1					45 min.
Puleo[102]	39	15-120 min.	90%	89%	
Myoglobin					30 min.
Zabel[95]	63	90 min.	94%	88%	
Troponin-T					elaborate
Zabel[95]	63	90 min.	80%	65%	

Biochemical assays measuring the rate of appearance of macro-molecules for early patency assessment.[95,97,98,102] N = the population size; time = the interval between the pre- and the post-treatment serum sample; Sens. = sensitivity, the ability to detect an angiographically reperfused infarct related artery; Spec. = specificity, the ability to correctly predict an angiographically occlude d infarct related artery; test = the "turn around" time needed for test measurements.

Figure 5



Serial assessment of serum creatine kinase (CPK) and myoglobin simultaneous with continuous vectorcardiographic registration of the ST-segment vector magnitude (ST-VM). The early rise of myoglobin is more rapid than that of creatine kinase and both coincide with rapid ST-VM recovery. A second small rise of myoglobin paralleled a re-elevation of the ST-segment, secondary to a reocclusion of the infarct related artery. Angio = angiography; PTCA = percutaneous transluminal coronary angioplasty; TIMI = thrombolysis in myocardial infarction flow grade. *Reprinted by permission of the American Journal of Cardiology, Klootwijk P, Cobbaert C, Fioretti P, Kint PP, Simoons ML; volume 72: pp 75G-84G, 1993. Copyright 1993. All rights reserved.*

not applicable either biochemical essays or arrhythmia monitoring would be a logical alternative. The integration of arrhythmia detection algorithms into an ST monitoring environment seems logical. Parallel application of ST monitoring, a 2-point biochemical assay, and/or arrhythmia monitoring might increase patency prediction accuracy,[91] would provide a back-up assessment in case of failure of one of the methods,[77] or might even give additional separate information.[103]

VIII: Other applications of ST-segment monitoring

The application of ischemia monitoring in acute myocardial infarction has been the focus of this thesis. Other possible applications include monitoring post coronary angioplasty (PTCA), detection of (silent) ischemia in unstable angina, chest pain evaluation, pre-hospital monitoring, and peri-operative monitoring.

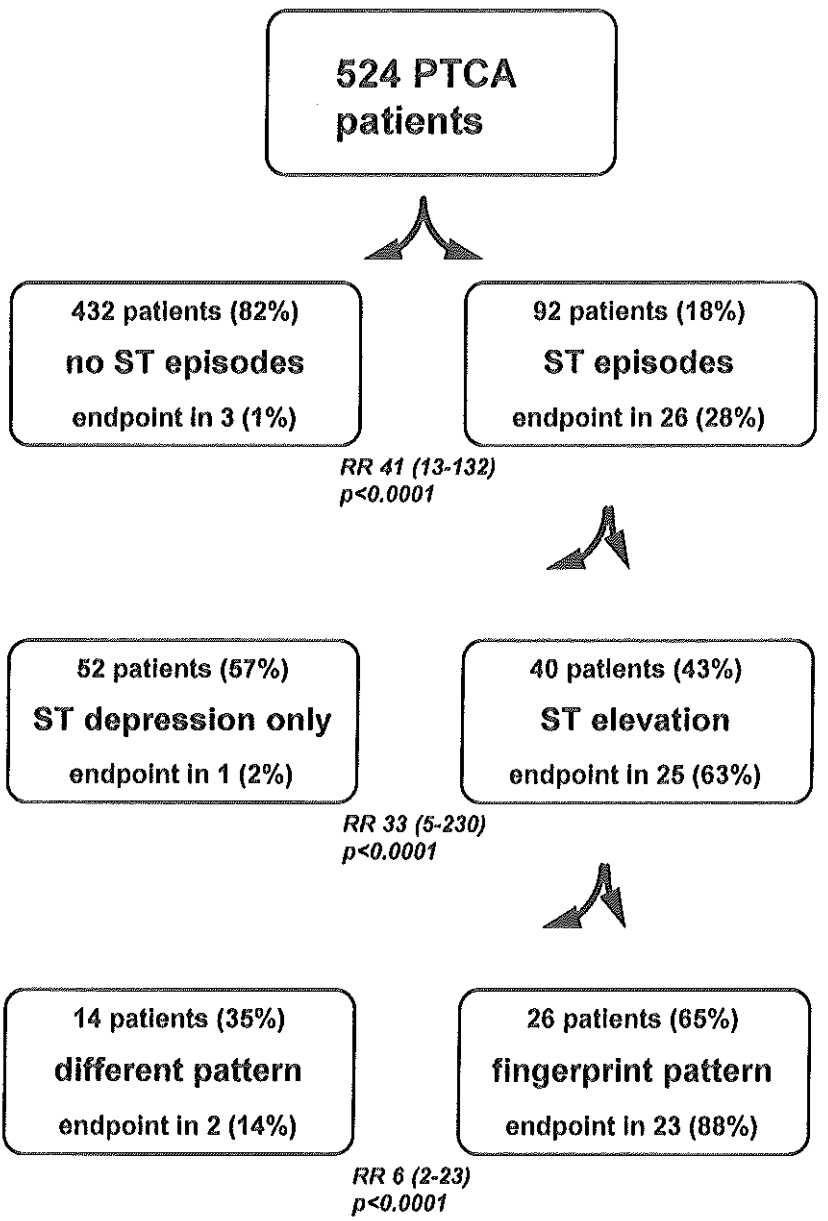
ST monitoring post coronary angioplasty

Ischemic episodes following coronary angioplasty (PTCA) are silent in approximately 50% of the patients and may become symptomatic after a prolonged silent episode.[104,105] Continuous multi-lead ST monitoring may be an early warning of (pending) coronary occlusion at the site of coronary angioplasty. The multi-lead ST deviation pattern recorded during the angioplasty induced coronary occlusion provides a patient and site specific "fingerprint" that will be reproduced whenever reocclusion occurs at the same site.[78,104-107] On the other hand, ST elevation in a different pattern most likely signifies occlusion at a different site, while ST depression usually reflects subendocardial ischemia, either in the perfusion area of the dilated vessel, or in a remote area. The importance of multi-lead monitoring was demonstrated in a series of 524 patients who underwent elective or emergency coronary angioplasty.[104] Figure 6 shows the occurrence of a combined clinical endpoint of untoward clinical events (acute myocardial infarction, urgent coronary artery bypass surgery, or death during hospitalization) related to the ST deviation pattern. In a smaller series of 200 patients monitored following elective PTCA 90% of patients with ST elevation had enzyme evidence of acute myocardial infarction versus 3% of patients with ST depression only.[105] In this series episodes of ST elevation were eventually accompanied by angina in 90% of cases, whereas only 41% of ST depression episodes were accompanied by angina. Amongst patients with ST elevation, detectable ST changes preceded angina by a mean of 45 min. (range 5 - 150). Thus, multilead monitoring does provide an early warning of vessel occlusion following PTCA, allowing early medical or mechanical intervention, potentially preventing acute myocardial infarction or limiting infarct size.

ST monitoring in unstable angina pectoris

Patients suffering unstable angina pectoris have a high risk of developing acute myocardial infarction, probably due to the same pathophysiological substrate of plaque disruption, leading to platelet activation, enhanced reactivity of the coronary smooth muscle, and eventually a shift of the coagulation balance toward thrombosis.[9,108-111] Unstable angina pectoris patients also have an increased risk of sudden death and life-threatening arrhythmias and frequently require urgent revascularization for persistence of symptoms under maximal medical treatment.[110-113] Unfortunately ischemia is most often silent: 80 to 95% of episodes occurring in more than half of the unstable angina patients.[112-116] Table 9 summarizes results

Figure 6



Occurrence of a combined clinical endpoint of untoward clinical events (acute myocardial infarction, urgent coronary artery bypass surgery, or death during hospitalization) related to ST deviation patterns recorded with continuous ST-segment monitoring following percutaneous transluminal coronary angioplasty (PTCA) in 524 patients. Fingerprint pattern = ST deviation pattern on multilead monitoring similar to the pattern occurring during the original coronary occlusion (PTCA). *Data reported by Krucoff et al..*[101]

Table 9

study	N	type UAP	TIE	silent TIE	outcome measure	with TIE	no TIE	P
Gottlieb[112]	70	CP at rest with ▵ ST	37 (53%)	90%	1 month			
					AMI	6/37	1/33	0.005
					CABG/PTCA	10/37	3/33	0.02
					total	16/37	4/33	0.02
					2 years			
					AMI or death	10/37	1/33	< 0.01
Langer[113]	136	CP at rest crescendo AP CP > 20 min.	89 (66%)	92%	in hospital			
					death or AMI	14/89	2/46	< 0.001
					CABG/PTCA	29/89	7/46	< 0.01
					total	43/89	9/46	< 0.005

Results of 2 studies investigating the occurrence and prognostic value of (silent) transient ischemic episodes (TIE) during bed rest in the coronary care unit for unstable angina pectoris (UAP).[112,113] ▵ ST = ST change ≥ 1mm. at qualifying ECG; AMI = acute myocardial infarction; CABG = emergency coronary artery bypass grafting; PTCA = emergency percutaneous transluminal coronary angioplasty.

of two investigations into the occurrence and prognostic significance of (silent) ischemia as recorded during acute coronary care for unstable angina pectoris.[112,113] The presence of transient ischemic episodes (TIE) strongly predicted an unfavorable outcome, most of them occurring early in the hospital course. Gottlieb and co-workers showed in a multivariate analysis that presence of (silent) TIE was the strongest predictor of an unfavorable outcome ($p < 0.002$), followed by chest pain during the first 2 days ($p < 0.02$). None of the other 13 tested demographic, clinical, electrocardiographic, or angiographic variables were significant in addition to these 2 variables.[112] Langer and co-workers prospectively confirmed that patients with a total duration of both silent and symptomatic TIE ('total ischemic burden') ≥ 60 minutes per 24 hours had a worse prognosis than patients with a shorter total ischemic burden.[113] Similar results regarding clinical outcome following unstable angina pectoris have been found for the presence of (silent) ischemia detected with pre-discharge ambulatory Holter ST-segment monitoring.[114,115]

Real-time multilead ST-segment monitoring may thus detect (silent) ischemia, identifying patients at high risk of sustaining a major cardiovascular event, and might be useful in guiding medical therapy and selection of high risk patients for angiographic evaluation. The use of multiple leads increases sensitivity for ischemia and enables the differentiation between transmural ischemia (ST elevation) and subendocardial ischemia (ST depression) and may thus be an early warning of an evolving acute myocardial infarction, thereby allowing early institution of thrombolytic therapy.[3,13,75,84,116,117] Strategies using real-time ST monitoring information in patient management remain to be tested however.

ST monitoring for chest pain evaluation

Patients without prior history of coronary disease who present at the emergency department with symptoms potentially due to unstable ischemic syndromes are generally evaluated by history and physical examination. Further examinations include the 12-lead ECG, chest X-ray, and laboratory tests.[111,118] When the ECG is non-diagnostic for ischemia and the other examinations are also non-indicative of cardiac disease the risk of complications is low and patients are discharged or admitted to a non-intensive setting such as a step-down unit or a general cardiology ward. Typically, subsequent ECGs and serum biochemical markers of cardiac necrosis are taken every 8 to 12 hours over the next 1 to 2 days. Evaluation may be shortened using continuous ST monitoring and the addition of exercise electrocardiography and (stress) echocardiography when indicated, to identify patients with a low risk of acute cardiac disease. Recently Gibbler and co-workers described their experience with continuous 12-lead electrocardiographic monitoring (ST100, Mortara Instrument, Milwaukee) in patients presenting to the emergency department with chest pain.[118] Visual inspection of the ST trend over time as well as individual ECGs was performed at regular intervals, looking for ST changes as well as Q-wave formation, R-wave amplitude loss, and T wave morphology changes. Out of the 384 patients evaluated according an intensive 9 hour protocol, 86 were eventually admitted to the cardiology department. On discharge 18 patients (21%) had diagnoses of cardiac disease after evaluation for acute myocardial ischemia and acute myocardial infarction. Continuous 12-lead ECG recordings detected ischemic changes in 7 out of 18, thus having a sensitivity of 39% (95% confidence interval 16 to 61%). Continuous 12-lead ECG monitoring lead

to a false positive prediction of acute ischemia in 10 of 366 patients eventually classified as having symptoms of non-cardiac origin, thus had a specificity of 97% (95% confidence interval 96% to 99%). The importance of the continuous 12-lead ECG recordings relative to the biochemical assays or the echocardiographic evaluation was not reported. While continuous ECG monitoring may detect all forms of ischemia, biochemical assays detect necrosis only. Previously it was shown that serial analysis of 12-lead ECGs taken at 3 to 4 hour intervals had a sensitivity of 39% for detecting acute myocardial infarction while sensitivity of serial CK-MB determinations was 68%.[119] Specificity of the 2 methods were 88% and 95% respectively. It was not reported whether these assessment methods identified the same patients or whether they were complimentary.

ST monitoring in the pre-hospital phase

Continuous 12-lead ECG recordings may be helpful in pre-hospital monitoring of patients suspected of having an acute myocardial infarction or other ischemic syndromes. Recent reports have advocated the pre-hospital administration of thrombolytic therapy to reduce the time between onset of symptoms and treatment.[120-124] In these studies the decision whether or not to treat a patient in the field was made on presence of symptoms, absence of contra-indications, and a conventional 12-lead electrocardiogram. In one study the decision was supported by an automated analysis of the 12-lead ECG by a portable electrocardiograph (Sicard P, Siemens Elema E.B., Solna, Sweden) which has the capability of automated serial ECG recording.[120] When major ST elevation was present thrombolytic therapy was initiated, otherwise the patient was re-evaluated at the hospital. Continuous registration of ECGs can be initiated in the pre-hospital phase to evaluate patients with equivocal electrocardiographic evidence of transmural ischemia. Especially when transient occlusion of the coronary artery is present the diagnosis of acute myocardial infarction might be missed by one or a few static 12-lead ECGs.[1,3,125] It is not known whether pre-hospital thrombolytic treatment is to be recommended in these patients, but the added information of continuous electrocardiographic monitoring will facilitate the decision making process once the patient has arrived in the emergency room. Of course the added value of continuous ECG registration as compared to a single ECG in the pre-hospital phase is greater when transport time of patients is longer, for instance when patients are transported from rural areas. Furthermore, accuracy of ST-segment recovery analysis for the purpose of noninvasive patency assessment depends on the continuous electrocardiographic registration initiated as early in the course of the evolving myocardial infarction as possible. The documentation of the dynamic ST changes in the early phase of acute myocardial infarction and the detection of the true peak amplitude will enhance accuracy of the noninvasive patency assessment.[6, 11, 12, 15, 18]

Peri-operative ST monitoring

Acute myocardial infarction and congestive heart failure are major contributors to peri-operative morbidity and mortality.[126,127] The entire period from the induction of anesthesia to recuperization is stressful, characterized by complex and rapidly changing responses that may be poorly tolerated by patients with coronary disease or a compromised left ventricular function. Factors that are liable for these rapid changes include depression of myocardial contractility and cardiac output by anesthetics, as well as fluctuations in arterial pressure, ventricular filling pressures,

blood volume, activity of the autonomic nervous system and body temperature. The absolute risk of cardiac adverse events depends on the type and duration of the operation, the type of anesthesia applied, and whether it is performed electively or under emergency conditions. There is a general increase in mortality of 25 to 50% in patients with underlying cardiovascular disorders relative to patients with a normal cardiac function.[127] Among the non-cardiac surgical procedures, the highest cardiovascular complication rates are seen in peripheral vascular surgery, especially in abdominal aortic aneurysm surgery, since such patients often have substantial coronary artery disease as well.[126-129] Their peripheral vascular disease may have led to a more sedate lifestyle in which exertion related symptoms of cardiac disease are not provoked. As a result, the extent of cardiac disease will be underestimated during history taking. The symptoms of peripheral vascular disease may also restrict the value of exercise electrocardiography to identify the patients with severe coronary artery disease.

Determining the risk factors for adverse peri-operative cardiac outcomes would allow the development of preventive strategies and a more efficient allocation of health care resources. Patients at high risk of adverse outcomes can be identified by a history of recent acute myocardial infarction or presence of congestive heart failure, while other pre-operative predictors remain controversial.[126,127] Specialized cardiac testing before surgery, such as dobutamine stress echocardiography,[130,131] dipyridamole-thallium scintigraphy,[128] and ambulatory electrocardiographic (Holter) monitoring,[126] may also identify patients with increased risk. It has been shown by Mangano and co-workers that continuous ischemia monitoring may be helpful prior to, during, and especially after surgery in men with a high risk of or known coronary artery disease undergoing non-cardiac surgery.[126] Of the 474 men included in the study, 83 or 18% had post-operative cardiac events during hospitalization: 15 had an ischemic event (cardiac death, myocardial infarction, unstable angina); 30 had congestive heart failure; and 38 had ventricular tachycardia. Post-operative myocardial ischemia was seen in 41% of the patients monitored with a 2-channel Holter recorder and was associated with a 2.8-fold increase in the odds of all cardiac outcomes (95% confidence interval 1.6 to 4.9; $p < 0.0002$) and a 9.2-fold increase in the odds of an ischemic event (95% confidence interval 2.0 to 42.0; $p < 0.004$). Many variables were univariately associated with adverse cardiac outcome, including a history of previous myocardial infarction, arrhythmias, congestive heart failure, claudication, or definite coronary artery disease, treated diabetes mellitus, use of digoxin, a serum creatinine ≥ 177 μmol/ liter, vascular surgery, risk scores, as well as ischemia on Holter monitoring prior to, during or after surgery. Multivariate analysis identified ischemia detected with Holter monitoring after surgery to be the only variable independently associated with ischemic events. Only ischemia on pre-operative Holter monitoring and the use of digoxin for congestive heart failure were predictors of ventricular tachycardia. Variables associated with congestive heart failure included a history of arrhythmia, medication treated diabetes mellitus, duration of anesthesia and surgery, vascular surgery, and the type of anesthetics used. This was the only outcome variable for which ischemia on Holter monitoring was no independent predictor. The Holter recordings revealed transient episodes of myocardial ischemia in 12 of 14 patients with adverse ischemic events, preceding any clinical evidence of these adverse

outcomes by at least 4 hours.

Pasternack and co-workers evaluated the value of peri-operative ischemia monitoring in 385 patients undergoing peripheral vascular surgery.[132] They showed a strong correlation between the total duration of ischemic events detected with a one channel (CM5) real-time ambulatory ECG recorder (QMED Monitor One Star, QMED Inc., Clark, N.J., U.S.A) and peri-operative myocardial infarction as well as late cardiac complications up to 2 years after operation. In multivariate analysis only age and the presence of peri-operative ischemic episodes during more than 1% of the monitoring time were independent predictors of peri-operative myocardial infarction as well as late cardiac events. Similarly, Landesberg and co-workers reported that long-duration (> 2 hours) postoperative ST-depression as recorded with a 3-channel Holter recorder was the only factor significantly associated with cardiac morbidity in 151 patients undergoing major vascular surgery.[129] Long duration ischemia preceded 85% of the 13 cardiac events (6 acute myocardial infarctions, 2 unstable angina, and 5 congestive heart failure).

It can be concluded that ischemia monitoring is a valuable predictor of adverse cardiac outcomes following major non-cardiac surgery, especially in patients at risk of or with proven coronary artery disease. Therapeutic trials in which care is guided by real-time ischemia monitoring are warranted to determine whether prevention or treatment of peri-operative ischemia can reduce cardiac morbidity or mortality.

IX: Areas for Future Research

The ST100 device has been developed as a mobile ST monitor and is therefore limited in its display capabilities. The option to link the device to a central monitoring network in which several beds can be monitored simultaneously, with real-time display of the wave-forms as well as trends of ST deviation over time and other analysis tools, has now overcome these restrictions. The possibility of real-time ST monitoring should be integrated in or be compatible with monitoring devices in other environments, including monitoring/defibrillator devices used during patient transport, emergency room and catheterization laboratory monitoring equipment, coronary care and intensive care unit monitoring systems and anesthesia monitoring equipment. To facilitate the analysis and comparison of electrocardiographic data over prolonged episodes under different circumstances a standard for data compression and the minimum amount of electrocardiographic and other information transferred should be set so that data can be transferred, appended, and compared regardless of the device they were recorded with. The similarities and differences in lead systems, signal processing and averaging, and data reduction and their influence on comparability of ST-segment monitoring data recorded with either Holter recorders, continuous vectorcardiography, or continuous 12-lead electrocardiography need to be addressed.[60,80]

The algorithm involved in the automated patency assessment should undergo further testing in patients suffering acute myocardial infarction, preferably including comparisons with simultaneous angiography. Optimum thresholds for the slope, recovery threshold, and minimum amplitude should be sought, potentially with infarction area specific algorithms to compensate for the reduced lower amplitudes encountered in inferior and especially posterior and lateral infarctions.[18,20]

So far the patency assessment algo-

rithms have not been validated in patients with conduction delays. Of special concern is the accuracy of the algorithm in patients with a left bundle branch block, in whom the repolarization phase is markedly distorted and the ST segment may display varying slopes depending on heart rate. The only study addressing the possibility of self referencing for detection of coronary occlusion during left bundle branch block used coronary angioplasty as a model in which only modest increases (median of 4 ± 3 beats/min) in heart rate were found during balloon induced coronary occlusion.[133] Whether self-referencing is able to compensate for the more dynamic heart rate changes observed during acute myocardial infarction remains to be investigated.

Combinations with arrhythmia monitoring and biochemical essays need to be explored. This may lead to improved accuracy, methods may provide a back-up assessment in case of failure or inapplicability of one of them, or might even give additional separate information.[77,91,103]

More quantitative approaches in addition to detection of patency of the infarct artery or the determination of speed and stability of reperfusion need to be sought. Continuous monitoring might improve definition of the maximum amount of ischemia in patients with cyclic reperfusion in whom a single or few static ECGs were taken during periods of actual ST recovery. The detection of extent of the ischemic area reflected in the number of leads with ST deviation could be improved similarly. The integration of the dynamics in severity and extent of ischemia over time as a time-severity index might help to clarify the response to treatment as a relationship among infarct related artery patency, the amount of myocardium salvaged, and clinical outcome. Relevance of this information should be related to and compared with other preferably noninvasive information. To develop such models will require a thorough process of statistical modeling or neural network development that includes other routinely available noninvasive descriptors to yield a practical probabalistic, patient specific prediction of infarct outcome.[77]

The physiology and clinical relevance of the different reperfusion patterns previously described by Dellborg and coworkers need to be investigated. Rapid resolution of ST elevation seems to signify reperfusion and persistent ST elevation failure to achieve reperfusion. Little is known about the clinical importance of cyclic reperfusion: recent publications have suggested that this phenomenon is associated with larger infarctions.[4,7] It is not known whether this is a causal relationship or whether this is largely due to the fact that cyclic reperfusion is more obvious when infarction generates higher ST-segment amplitudes. The relevance of an increased ST elevation prior to ST recovery ("late peak pattern")[6] is also unknown. Some authors have suggested that the late elevation is related with larger infarctions or less myocardial salvage, possibly due to reperfusion injury.[134-137] Another explanation however is that the late peak pattern represents a variation of the cyclic reperfusion pattern in a patient in whom ST monitoring was initiated after one or multiple previous ST elevation and recovery episodes.[6] Knowing what these patterns actually represent might enable better guidance of therapy. The physiologic reasons for discrepancies between continuously updated ST-segment recovery analysis and angiographic patency assessment need to be explored.[13] While this may be partly due to threshold and timing problems, other explanations may be found. Development of collateral flow may result in ST-recovery while the infarct related

Occlusion at a microvascular level may explain persistent ST elevation while the infarct related ar-tery is patent. The functional sufficiency of TIMI 2 flow remains debated.[51,138,139] In these patients the presence or absence of ST recovery may be of prognostic importance.

Most importantly, it needs to be assessed whether continuous ST-segment monitoring is helpful in patient triage in various unstable coronary syndromes. Its value depends on the accuracy of the information provided as well as on whether alternative therapeutic strategies indeed show to be beneficial. This is particularly true for rescue strategies for failed reperfusion through the infarct related artery, treatment strategies for (silent) ischemia in unstable angina pectoris, coronary occlusion following PTCA, and treatment of ischemia during peri-operative monitoring in major (vascular) surgery. Studies addressing these issues are needed.

X: Conclusion

Continuously updated ST-segment recovery analysis is a useful noninvasive patency assessment technique, allowing the identification of failed or unstable reperfusion and recurrent occlusion with reasonable accuracy following thrombolytic therapy for acute myocardial infarction. This technique requires frequent ECG acquisition over multiple leads, with real-time accessibility. This may be facilitated by automated electrocardiographic devices such as the ST100 device (Mortara Instrument, Milwaukee) described in this thesis. Although improvements may be possible in several areas, this technique may now be used to select patients for studies assessing rescue strategies in case of failed or unstable reperfusion or recurrent occlusion.

Continuously updated ST-segment recovery analysis as an endpoint in acute myocardial infarction trials comparing treatment strategies aimed at early stable reperfusion of the infarct related artery deserves exploration. It needs to be investigated which parameter is prognostically more important: time to first evidence of reperfusion, time to stable reperfusion, or presence of recurrent occlusion.

ST monitoring may also be useful in other circumstances such as: post angioplasty, unstable angina pectoris, chest pain evaluation, pre-hospital monitoring, and peri-operatively. Application of ST monitoring in these syndromes requires further development.

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SUMMARY

Chapter 1
An introduction to the history of electrocardiography and the physiology of ST elevation as a marker of transmural ischemia due to infarct related artery occlusion is presented. Continuous digital multi-lead ST segment monitoring and its major applications are briefly described.

Chapter 2
A total of 44 angiographic observations in 22 patients were compared with noninvasive patency assessments by continuously updated ST-segment recovery analysis using continuous 12-lead ST monitoring. Sensitivity of the noninvasive method for an occluded infarct related artery was 90% and specificity was 92%. Of the 22 patients, 11 (50%) had ST evidence of cyclic reperfusion prior to angiography. In 5 patients (31%) cyclic reperfusion was recorded before treatment onset. Since static patency assessments cannot describe this behavior, 3 additional parameters describing the speed, stability, and duration of ST-recovery are proposed.

Chapter 3
Inter- and intra- observer variation for 3 readers was assessed for continuously updated ST-segment recovery analysis. A high level of concordance was found in and between readers for patency assessments 90 minutes after onset of thrombolytic treatment, with Kappa values of 1.0 for intra-observer variation and 0.79 to 0.93 for inter-observer variation. Patency assessments 6 hours after onset of thrombolytic therapy showed a slight reduction in Kappa values, although concordance overall remained high. Similar results were found for the number of ST recovery and/or re-elevation events, and for continuous assessments comparing each minute of the recording. Sources of variability included differences in interpretation of low ST amplitude ECGs with relatively high noise content, anterior ST-segment depression, and gaps in the ST recording, as well as operator fatigue. Thus, continuously updated ST-segment recovery analysis can be ensued to a high level of intra- and inter-observer consistency.

Chapter 4
Essential principles of the continuously updated ST-segment recovery analysis described in Chapter 2 were modified into an automated patency assessment program and incorporated into the ST monitor itself. The algorithms and definitions of measurement ECGs, as well as the operator interactions required, are described.

Chapter 5
The automated patency assessment method described in Chapter 4 detected all 35 angioplasty balloon inflations causing ≥ 200 μV peak ST elevation. In addition all 5 inflations with < 200 μV peak ST elevation preceded by an inflation causing ≥ 200 μV were detected. Occlusion was detected a median of 40 seconds after inflation, reperfusion a median of 17 seconds after deflation. The requirement of ≥ 200 μV ST elevation measured in at least 1 ECG prior to or at the moment of assessment introduced a bias favoring detection of LAD occlusions over RCA occlusions, and both over LCX occlusions.

Chapter 6
Patterns of ST deviation were related to the angiographically determined infarct related artery. Of the patients with the right coronary artery as the infarct related artery, 87% had lead III as the most elevated lead. Leads V2-V4 were the peak lead

in 98% of the patients with occlusion of the left anterior descending artery. Location of the peak lead was inferiorly and apically in patients with a left circumflex artery occlusion. Combining leads III, V2, and V5 would record at least 1 lead with ≥ 200 μV ST elevation in 321 out of 361 or 89% of the patients. A 3 lead system with inferior, anterior, and apical lead orientations should be adequate to record at least one lead with sufficient ST deviation. Twelve-lead or vectorcardiographic ST-monitoring systems will increase sensitivity for ST deviation especially in smaller infarcts and will facilitate comparison of the ST deviation pattern during recurrent ST elevation with the primary ST elevation episode to assess whether it indeed signifies recurrent occlusion of the infarct related artery.

Chapter 7
Continuously updated ST-segment recovery analysis in conjunction with frequent electrocardiographic acquisition allows accurate, noninvasive assessment of the perfusion status of the infarct area over time. It gives more information than "snap-shot" assessments made with coronary angiography. It may be helpful in selecting patients with failed or unstable reperfusion for trials testing more aggressive secondary revascularization strategies. More knowledge is needed about the clinical and physiological meaning of ST-segment evidence of extent, severity, and duration of ischemia, and the stability of reperfusion. Continuously updated ST-segment recovery analysis might than be used as an important noninvasive endpoint in acute myocardial infarction trials.

Chapter 8
Continuous 12-lead ECG recordings were reviewed in 40 patients in whom a perfusion balloon catheter (PBC) was used to stabilize an intimal dissection following a routine angioplasty procedure with a conventional balloon PTCA. Comparing PBC with PTCA median single lead peak ST deviation were 132 versus 321 μV ($p = 0.0001$), median extent of leads with new ST elevation were 0 versus 3 leads ($p = 0.0001$), and the total summated absolute ST deviation over all 12 leads over the entire balloon inflation duration were 1083 versus 1173 μVmin (NS). Thus, despite the fivefold longer PBC balloon inflations, severity and extent of ST elevation were significantly reduced, but ischemia was not entirely eliminated.

Chapter 9
Accuracy of patency prediction was assessed in 82 acute myocardial infarction patients for the continuously updated ST-segment recovery analysis and 5 methods using static electrocardiograms. Accuracy (95% confidence interval) was 85% (77-93%) for the continuous method, and 68% (57-78%), 78% (69-87%), 83% (74-91%), 82% (73-90%), and 80% (71-89%) for the static methods. At the moment of angiography a median of 2 hours following onset of thrombolytic treatment the most accurate static method and the continuous method agreed in 90% of patency assessments. Agreement was reduced to 83% when patency assessments were performed earlier at 90 minutes following treatment onset, and to 77% at 60 minutes. Early disagreement was mainly seen when the continuous ST recording showed ST recovery from a delayed peak ST elevation after the pre-treatment static ECG or when dynamic ST changes suggesting cyclic reperfusion occurred. Such findings occur in approximately 50% of patients treated with thrombolytic therapy. Thus, the continuous method is as accurate as the static methods when compared to angiography 2 hours following treatment onset. The continuous updating of reference

points appears to provide important additional information early following thrombolytic therapy, when ST behavior is more dynamic.

Chapter 10

Intermittent reperfusion has consistently been reported to occur in approximately 37% of acute myocardial infarction patients treated with thrombolytic therapy and seems to be related to unfavorable outcomes. A reliable, noninvasive assessment technique able to detect both failed and unstable reperfusion would therefore be useful. For this reason continuously updated ST-segment recovery analysis has been developed. It has been shown to be a practical noninvasive patency assessment technique with acceptable accuracy.

Possible treatment options that could be chosen depending on the reperfusion behavior as evidenced by continuously updated ST-segment recovery analysis are discussed, including: discontinuation of thrombolytic therapy when reperfusion has occurred; addition of anti-coagulants or new platelet inhibitors when intermittent reperfusion occurs; repeat administration of thrombolytics for failed or recurrent occlusion; and urgent angiography with PTCA for failed or recurrent occlusion. Many of these options are under debate or have not yet been investigated, partly because a practical (continuous) noninvasive patency assessment method was not available.

The use of ST monitoring in clinical trials comparing drug regimens aimed at early stable reperfusion is discussed. Main outcomes of the GUSTO-1 ST-segment monitoring substudy, the first large scale attempt to compare speed and stability of reperfusion as assessed with continuously updated ST-segment recovery analysis in 4 different thrombolytic regimens, are presented.

ST monitoring may help determine the prognosis of individual acute myocardial infarction patients. A very low risk of complications could for instance result in a shorter stay at the coronary care unit, followed by an earlier discharge.

Other noninvasive patency assessment methods are described and compared with continuously updated ST-segment recovery analysis. Accelerated idioventricular rhythm (AIVR) is a specific but infrequently occurring marker of reperfusion. It does not indicate recurrent occlusion. AIVR is therefore not useful as a single marker of failed or unstable reperfusion. Several biochemical assays have been developed for early detection of failed reperfusion. They currently provide a static assessment only, no distinction is made between stable versus unstable reperfusion and detection of recurrent occlusion depends on other assessments. Parallel application of ST monitoring, a 2-point biochemical assay, and/or arrhythmia monitoring might increase patency assessment accuracy, would provide back-up assessment in case of failure of one of the methods, or might even give additional separate information.

ST monitoring may also be useful in other circumstances such as: post angioplasty, unstable angina pectoris, chest pain evaluation, pre-hospital monitoring, and peri-operatively. Application of ST monitoring in these syndromes requires further development.

SAMENVATTING

Hoofdstuk 1

De Engelse fysioloog Augustus Désiré Waller (1856 - 1922) maakte met een capillaire electrometer de eerste registraties van de electrische activiteit van het menselijke hart gemeten vanaf de borstwand. De Leidse hoogleraar in de fysiologie Willem Einthoven (1860 - 1927) was ontevreden met de kwaliteit van de registraties met dit ongevoelige instrument en ontwikkelde daarom een meer gevoelige snaar-galvanometer. Hij introduceerde de term electrocardiogram (EKG, ECG), noemde de achtereenvolgende uitslagen P, Q, R, S en T, en introduceerde de standaardafleidingen I, II en III. Voor het ontwikkelen van de techniek en het ontdekken van de mechanismen achter het ECG ontving hij in 1924 de Nobel-prijs voor geneeskunde.

Fred H. Smith toonde in 1918 aan dat ST-segment elevatie het gevolg was van afsluiting van een van de kransslagaderen. ST elevatie is het gevolg van verschil in rust- en activerings- potentialen tussen de transmurale ischaemische zone en het niet ischaemische deel van de hartspier. Ongeveer 75% van de patienten met een acuut myocard infarct hebben ST elevatie op hun ECG door afsluiting van een van de kransslagaderen, meestal door een thrombus. Zonder reperfusie door de infarct-gerelateerde kransslagader vermindert de ST elevatie geleidelijk in de navolgende uren tot dagen door het afsterven van de ischaemische myocard cellen. Als er echter reperfusie plaats vindt, dan treedt er een versnelde normalisering van het ST-segment op. Continue ECG registratie voor het vervolgen van de ST elevatie ("ST bewaking") kan dan ook op niet-invasieve wijze een adequaat inzicht geven in het wel of niet succesvol zijn van therapieën gericht op reperfusie.

Het "Ischemia Monitoring Laboratory" van de Duke University Medical Center in Durham, Verenigde Staten, heeft in samenwerking met de firma Mortara Instrument in Milwaukee een apparaat ontwikkeld voor continue digitale 12-afleidingen electrocardiografie (ST100). Dit apparaat is gericht op de onmiddelijke ST-segment bewaking en analyse aan het bed, zodat de behandeling van het acute myocard infarct gestuurd kan worden op basis van kennis over het wel of niet succesvol zijn van de reeds ingestelde behandeling. Dit proefschrift is het gevolg van mijn activiteiten als een "research fellow" aan de Duke University, waar ik mij bezig hield met de ontwikkeling en toetsing van apparatuur, programmatuur, alsmede klinische toepassingen voor ST bewaking.

Hoofdstuk 2

In 22 patienten werden 44 angiografische bepalingen gedaan van de infarct-gerelateerde kransslagader doorbloeding en deze vergeleken met gelijktijdige non-invasieve bepalingen, gedaan met de continu bijgestelde ST-segment normalisering bepalings-methode. Hierbij werd gebruik gemaakt van continue digitale 12-afleidingen ECG registratie met de ST100 electrocardiograaf. De non-invasieve methode had een sensitiviteit voor een afgesloten kransslagader van 90% en een specificiteit van 92%. Van de 22 patienten toonden er 11 tekenen van intermitterende reperfusie in hun continue ST registratie voordat angiografie plaats had gevonden. Vijf patienten toonden intermitterende reperfusie voordat thrombolyse was aangevangen. Statische bepalingen van de kransslagader doorbloeding kunnen dit gedrag niet registreren, daarom werden 3 nieuwe parameters voorgesteld ter beschrijving van de snelheid, stabiliteit en duur van ST normalisatie.

Hoofdstuk 3
Voor de continu bijgestelde ST-segment normalisering bepalings-methode werden de inter- en intra- waarnemers variatie bepaald tussen 3 waarnemers. De concordanties tussen waarnemers en binnen een waarnemer voor non-invasieve bepalingen van kransslagader doorbloeding 90 minuten na aanvang van thrombolyse waren hoog, met Kappa waarden van 1,0 voor intra-waarnemer variatie en tussen 0,79 tot 0,93 voor inter-waarnemer variatie. Dezelfde bepalingen voor 6 uur na begin van behandeling lieten een geringe afname in Kappa's zien, hoewel de concordantie over het geheel genomen hoog bleef. Vergelijkbare uitkomsten werden gezien voor bepalingen van het aantal malen dat ST normalisatie en re-elevatie optrad en voor de continue bepalingen waarin iedere minuut van iedere opname met elkaar werd vergeleken. Oorzaken van variabiliteit waren: de interpretatie van ECG's met een hoog "ruis" gehalte; voorwand ST depressie; onderbrekingen in de ST registratie; alsmede de vermoeidheid van de waarnemer. Geconcludeerd wordt dat continu bijgestelde ST-segment normaliserings bepalingen gedaan kunnen worden met een hoge mate van concordantie tussen waarnemers en binnen een waarnemer.

Hoofdstuk 4
Principes van de continu bijgestelde ST-segment normalisering bepalings-methode, zoals beschreven in hoofdstuk 2, werden gemodificeerd, zodat deze non-invasieve methode kan functioneren als een geautomatiseerde procedure. De geautomatiseerde methode diende uitgevoerd te kunnen worden binnen de continue digitale 12-afleidingen electrocardiograaf. De gebruikte algorithmes en de definities voor de selectie van ECG's welke gemeten en vergeleken worden, alsmede de interacties welke nodig zijn om de geautomatiseerde procedure te laten verlopen, worden hier beschreven.

Hoofdstuk 5
De geautomatiseerde procedure voor non-invasieve bepaling van de kransslagader doorbloeding werd getest tijdens percutane transluminale coronair angioplastie (PTCA). Alle ballon inflaties die door afsluiting van de kransslagader een ST elevatie ≥ 200 μV veroorzaakten werden herkend. Verder werden alle ballon inflaties met een ST elevatie < 200 μV herkend die vooraf waren gegaan door een ballon inflatie met ≥ 200 μV piek ST elevatie. De kransslagader afsluiting werd na een mediane duur van 40 seconden herkend, reperfusie na deflatie van de ballon na een mediane duur van 17 seconden. De in de algoritmes ingestelde voorwaarde dat er minimaal één ECG voor het moment van bepaling moet zijn die ≥ 200 μV ST elevatie vertoont, veroorzaakt een selectie ten gunste van herkenning van LAD afsluitingen ten opzichte van RCA afsluitingen. Beiden worden beter herkend dan LCX afsluitingen.

Hoofdstuk 6
Patronen van ST deviatie op het 12-afleidingen ECG werden vergeleken met de angiografisch bepaalde infarct-gerelateerde kransslagader (RCA, LAD, LCX) in 361 patienten. Van de patienten met een RCA afsluiting hadden 87% de meeste ST elevatie in afleiding III. De meeste ST elevatie werd gezien in afleidingen V2-V4 in 98% van de patienten met een LAD afsluiting. De meeste ST elevatie bevond zich in een van de onderwands- of apicale- afleidingen in patienten met een LCX afsluiting. Een combinatie van afleidingen III, V2 en V5 zou ten minste één afleiding met ≥ 200

μV ST elevatie hebben in 321 van de 361 patienten (89%). Een ECG afleidingen systeem met oriëntaties naar de onderwand, voorwand en apex zal daarom adequaat zijn voor de detectie van ST elevatie in veel van de patienten geselecteerd voor thrombolyse. Vectorcardiografische of twaalf afleidingen ECG systemen kunnen de sensitiviteit voor ST elevatie verhogen, met name bij kleinere infarcten. Beide systemen zijn ook geschikter voor vergelijking van ST re-elevatie patronen met de oorspronkelijke ST patronen, zodat bepaald kan worden of het inderdaad om een hernieuwde afsluiting van de infarct gerelateerde kransslagader gaat.

Hoofdstuk 7
Continu bijgestelde ST-segment normaliserings bepalingen met behulp van frequent genomen ECG's zijn in staat om met bruikbare precisie non-invasieve achtereenvolgende bepalingen van de kransslagader doorbloeding te doen. Door deze achtereenvolgende bepalingen is het mogelijk een betere indruk te krijgen over de snelheid en stabiliteit van reperfusie. Hierdoor is het mogelijk patienten te herkennen bij wie geen of intermitterende reperfusie is opgetreden na thrombolyse, hetgeen niet mogelijk is met enkelvoudige angiografie. Deze patienten met onvoldoende resultaat van initiele thrombolyse kunnen dan geselecteerd worden voor vergelijkend onderzoek met meer agressieve strategieën gericht op stabiele reperfusie. Meer kennis is nodig omtrent de klinische en fysiologische betekenis van omvang, ernst, alsmede de duur van ischaemie, en de stabiliteit van reperfusie. De continu bijgestelde ST-segment normalisering bepalings methode kan dan gebruikt worden als een belangrijk non-invasief eindpunt in acuut myocard infarct onderzoek.

Hoofdstuk 8
Continue 12-afleidingen ECG registraties van 40 patienten bij wie een perfusie ballon catheter (PBC) was gebruikt ter stabilisering van een intima dissectie na standaard procedures met een conventionele PTCA ballon. PBC inflaties veroorzaakten een mediane ST deviatie van 132 μV ten opzichte van 321 μV bij conventionele PTCA ($p = 0,0001$). Het mediane aantal afleidingen met ST elevatie was 0 ten opzichte van 3 afleidingen ($p = 0,0001$), en de totale ST deviatie over 12 afleidingen gesommeerd over de gehele ballon inflatie was 1083 ten opzichte van 1173 μVmin (NS), respectievelijk. Hieruit blijkt dat ondanks vijfvoudig langere PBC inflaties de ernst en omvang van ST afwijkingen significant waren verminderd, maar ischaemie niet totaal verdwenen was.

Hoofdstuk 9
Een vergelijking van de nauwkeurigheid waarmee non-invasieve bepalingen van kransslagader doorbloeding gedaan kunnen worden met de continue bepalings methode en 5 statische ECG methoden werd uitgevoerd in 82 patienten met een acuut myocard infarct. Nauwkeurigheid (95% betrouwbaarheids interval) op het moment van angiografie was 85% (77-93%) voor de continue methode en 68% (57-78%), 78% (69-87%), 83% (74-91%), 82% (73-90%), and 80% (71-89%) voor de statische ECG methoden. Op het moment van angiografie, 2 uur na aanvang van thrombolyse, was er overeenkomst in bepaling tussen de continue methode en de beste van de statische methode in 90% van de patienten. Bij eerdere bepalingen 90 minuten na aanvang van thrombolyse was dit gereduceerd tot 83% en tot 77% bij bepalingen 60 na minuten. Een verschil in bepalingen werd met name gezien na het

optreden van een verlate piek in de ST elevatie en bij intermitterende ST elevatie. Deze 2 patronen werden gezien in ongeveer 50% van de patienten.

Geconcludeerd werd dat de continue methode even nauwkeurig is als de statische ECG methoden bij vergelijking met angiografie 2 uur na aanvang van thrombolyse. De continue methode lijkt belangrijke meerwaarde te hebben vroeg na aanvang van thrombolyse, wanneer het beloop van de ST elevatie meer dynamisch is.

Hoofdstuk 10

Intermitterende reperfusie treedt op in 37% van de patienten die thrombolyse ondergaan voor een acuut myocard infarct. Dit verschijnsel lijkt te resulteren in ongunstige uitkomsten na het acuut myocard infarct. Daarom is een betrouwbare non-invasieve techniek nodig die in staat is patienten te herkennen waarbij geen of intermitterende reperfusie is opgetreden. Voor dit doel is de continu bijgestelde ST-segment normalisering bepalings-methode ontwikkeld, waarvan aangetoond is dat het een praktische methode is met bruikbare precisie.

Afhankelijk van het reperfusie gedrag na thrombolyse, welke herkend wordt met de continu bijgestelde ST normaliseringsmethode, kan gekozen worden voor verschillende aanvullende of andere behandelingen. De volgende opties worden besproken: het stoppen van toediening van thrombolytica bij het optreden van reperfusie; de toevoeging van anti-coagulantia of nieuwe plaatjesremmers bij intermitterende reperfusie; herhaalde toediening van thrombolytica indien er geen reperfusie optreedt, of bij re-occlusie; spoed angiografie en PTCA voor persisterende occlusie of re-occlusie. Veel van deze opties zijn nog ter discussie of zijn nog niet onderzocht, mede door een gebrek aan praktische non-invasieve bepalingen.

De toepassing van continue ST bewaking in klinische studies wordt in dit proefschrift beschreven. Vooral onderzoeken naar strategieën gericht op vroege en stabiele reperfusie kunnen van deze toepassing gebruik maken. De belangrijkste resultaten van de GUSTO-1 ST-segment bewakings studie worden gepresenteerd. Dit is de eerste studie waarin 4 verschillende thrombolyse regimes worden vergeleken in de snelheid en stabiliteit van reperfusie.

ST-segment bewaking kan gebruikt worden voor het bepalen van de prognose na het acute myocard infarct. Laag risico patienten kunnen eerder van de CCU naar de afdeling worden overgeplaatst, met daarop volgend een vroeger ontslag.

Andere non-invasieve bepalingen van reperfusie worden beschreven en vergeleken met ST-segment bewaking. Versneld idioventriculair ritme (AIVR) is een specifieke maar weinig optredende marker van reperfusie. Bovendien kan AIVR intermitterende reperfusie niet herkennen. Daarom is AIVR niet geschikt als een alleenstaande non-invasieve bepalingsmethode. Verschillende biochemische bepalingen zijn ontwikkeld voor de non-invasieve bepaling van reperfusie. Ook deze methoden zijn statisch van karakter: er wordt geen onderscheid gemaakt tussen intermitterende en stabiele reperfusie. Bovendien kunnen ze geen re-occlusie herkennen. Het gelijktijdig vervolgen van het ST-segment, het bewaken van het hartritme en het doen van biochemische bepalingen kan de precisie van non-invasieve reperfusie detectie verhogen, een alternatief bieden als een van de methoden niet toegepast kan worden, of mogelijk aanvullende informatie opleveren.

Tenslotte worden andere toepassingen van ST-segment bewaking en registratie

beschreven. Dit kan bruikbaar zijn in de bewaking na PTCA, tijdens onstabiele angina pectoris, voor de bewaking tijdens transport van patienten naar het ziekenhuis, en voor de peri-operatieve bewaking van patienten met kransslagader vernauwing. Toepassingen van ST bewaking tijdens deze omstandigheden dienen verder ontwikkeld te worden.

ACKNOWLEDGEMENTS

At this point, having finished this thesis, I would like to take the opportunity to express my gratitude to all that have supported me on the road to completion.

First, I would like to thank Dr.K. Meeter, who guided me on my first steps into clinical research, which she did with great enthusiasm. It was through her that I was introduced to Professor M.L. Simoons, who in turn launched me into the ST monitoring project at Duke. I am extremely grateful for the trust I received from him, even though he hardly knew me. His guidance throughout my years abroad and his help in the synthesis of this dissertation after my return were essential.

My mentor at the Duke University Medical Center "candy store" was Mitchell Krucoff, director of the Ischemia Monitoring Laboratory. He gave me the freedom and support needed to roam around and prevented me from picking too many goodies at the same time. Mitch, thank you so much for providing this opportunity. Those two-and-a-half years were an experience Michèle and I will cherish for the rest of our lives. An important part of that wonderful experience were the nurses, technicians, statisticians, and secretary of the Ischemia Monitoring Laboratory: Sharon, Jill, Kathleen, Suzanne, Beverly, Helen, Karen, Cindy, Nancy, and Gail. I will not forget their help in getting me settled in Durham, the introduction into the world of ST monitoring, assistance in data-gathering, and all the other times they were of invaluable importance.

All co-authors deserve my gratitude for their outstanding effort, constructive criticism, and perseverance along the way. Some of them I would like to mention and thank in particular: Rob Califf, for keeping a watchful eye on the many projects we worked on and for his participation in the committee; David Mortara, his knowledge, interest, and participation in the ST monitoring project was and is indispensable; and Jim Pope, for creating and re-writing his excellent ST-3D analysis software until it met all of our specifications, especially because it absorbed the free hours outside his busy clinical practice.

I would also like to thank Galen Wagner for teaching me some of the basics in manuscript writing, ECG interpretation, and the warm support Michèle and I received.

The last mile is the hardest to run. If it were not for the help of Marianne Eichholtz, Anneke Kooijman, and Lilian Oelius it would have lasted so much longer. Thanks for assisting me in planning and meeting all the deadlines, in completing the paperwork and other requirements involved in a dissertation defence.

I appreciate the leeway that was given to me by the associates and fellows of the Internal Medicine Department at the St. Clara Hospital; it would have been extremely difficult to accomplish this goal without it.

As in every part of life, family and friends made this effort more enjoyable. It is impossible to mention each of you and all the ways in which you brightened the trail. Thanks to you all.

Dearest Michèle, since we met almost a decade ago you have inspired me. Your loving support helped me overcome many obstacles, without it this thesis would have been impossible. I dedicate this thesis to you.

CURRICULUM VITAE

Rolf Frederik Veldkamp was born on June 1, 1963 in Vleuten - De Meern, The Netherlands. In 1982 he completed his high school education at the Montessori Lyceum Herman Jordan, Zeist. He studied chemical technology at the Technische Hogeschool Delft until 1983. Subsequently he enrolled medical school at the Erasmus University Rotterdam. Doctoral examinations were passed in 1988 and the licensing examinations in 1990. Professor M.L. Simoons then introduced him to Doctor M.W. Krucoff and Professor R.M. Califf for a Research Fellowship in Cardiovascular Medicine at the Duke University Medical Center, Durham, North Carolina, USA. This fellowship focussed on the development and application of continuous digital 12-lead ST-segment monitoring, with special attention for its use in acute myocardial infarction. In the summer of 1993 he returned to Rotterdam, after which he worked as a resident in Cardiology at the St. Clara Hospital. His training in Internal Medicine started in October of the same year under Doctor A.F. Grootendorst. His training in Cardiology at the Thorax Center of the Academic Hospital Rotterdam "Dijkzigt" under Professor J.R.T.C. Roelandt will begin in October 1995.

The financial support of the following companies is gratefully acknowledged:

Mortara Instrument, Genentech, Eli Lilly, Alpha Therapeutics, Boehringer Ingelheim, Bristol-Meyers Squibb, Lorex Synthélabo, Sanofi Winthrop, Knoll, Zeneca Farma.