

Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO) ECG-monitoring Substudy

Study Design and Technical Considerations

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Trials comparing thrombolytic agents during acute myocardial infarction have generally focused on angiographic patency, left ventricular function, and mortality as endpoints of efficacy. The conduct of such trials is hampered by the need for invasive procedures or huge patient numbers in order to define such endpoints and achieve statistical power. The interpretation of such trials has also been a source of considerable controversy, since the results have not always supported the intuitive hypothesis that rapid, stable reperfusion of the infarct vessel should lead to interruption of infarction, myocardial salvage, improved left ventricular function, and better survival.

Dramatic ST-segment changes following thrombolytic therapy have repeatedly been correlated with reperfusion of the infarct artery.¹⁻¹⁷ When recorded continuously, over 30% of patients have ST-segment changes suggesting cyclic variations in coronary flow.^{1,2,10-12,14-17} As shown in Figure 1, an angiographic "snapshot" during periods of cyclic flow could obscure the relationship between drug treatment and the timing and stability of perceived patency. Static angiographic assessment of the infarct artery during cyclic flow periods could also obscure

the relationship between perceived patency and outcome variables, such as left ventricular function and mortality.

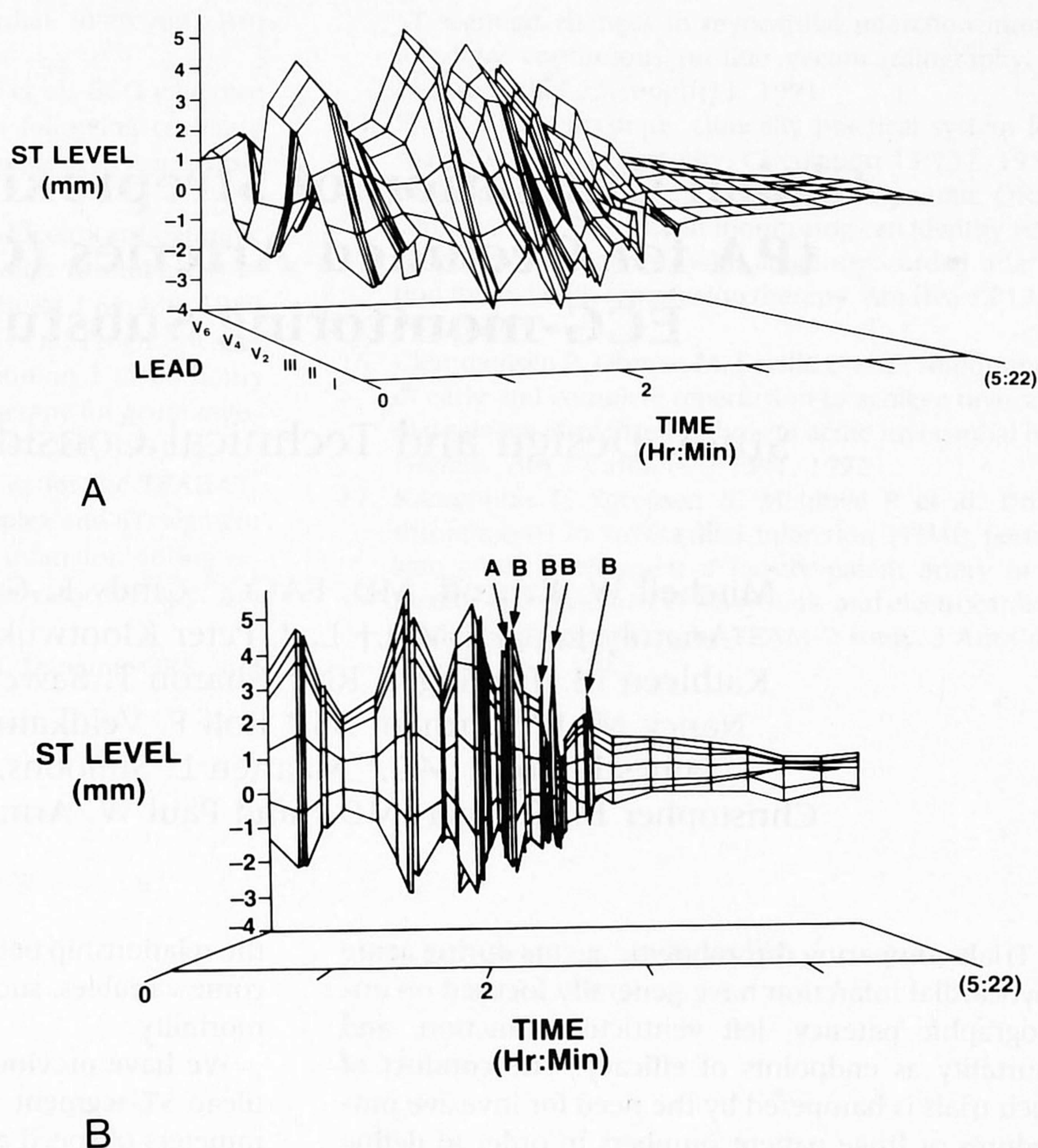
We have previously proposed a method for multilead ST-segment recovery analysis to quantify parameters of speed and stability of reperfusion.¹⁶ The technical development of this method has pursued the integration of electrocardiographic interpretation over the time domain,¹⁸ the articulation of the related heuristic principles of ST recovery interpretation using clinical trial designs with nonelectrocardiographic gold standards,¹⁹ and the derivation of the logistic principles underlying the heuristic process for device algorithm development and testing.²⁰ The clinical development of the method has been focused on real-time application, with a continuously updated correlation to simultaneous infarct artery patency, and on continuous characterization of the overall response to therapy, which appears to be somewhat independent of static angiographic assessments.¹⁶ The predictive information content of the method as a real-time marker of infarct artery patency has been investigated in a large, prospective, blinded trial.¹⁷ The continuous characterization of the ST-segment recovery process has been reported to correlate with mortality outcome,²¹ but more work is necessary to determine the utility of the method to compare and contrast therapeutic regimens for clinical or investigational purposes.

The Global Utilization of Streptokinase and tPA for Occluded arteries (GUSTO) electrocardiographic-

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Fig. 1. Continuous 12-lead ST-segment study from a patient presenting with inferior infarction with multiple cyclic flow changes. (A) Three-dimensional graphic presentation of ST deviation (y axis) for each of the precordial leads (x axis) over time (z axis), rotated to 60° orientation to illustrate fluctuations in inferior lead ST elevation. (B) Same patient, same graphic format at 90° orientation to emphasize fluctuation of ST levels over time, suggesting cyclic flow changes. Angiography (A) at the indicated peak showed an occluded right coronary. Subsequent reperfusion and reocclusion-induced ST fluctuation were caused by inflations/deflations of the angioplasty balloon (B). (*Figure continues*)



monitoring substudy was designed to pursue both technical and clinical investigational directions. First, the speed and stability of reperfusion, as quantified by continuous ST-segment recovery analyses, were used to compare tPA- versus streptokinase-containing thrombolytic regimens. Second, correlations with simultaneously acquired angiographic patency assessments during acute infarction were available to further expand on previous insights using a unique patient population. Third, to accommodate the logistic requirements necessitating the use of three different ST-segment devices (Holter, vectorcardiographic, and electrocardiographic) at different sites, a comparison of ST recovery parameters using a non-electrocardiographic gold standard was formally pursued as an ancillary experience.

Materials and Methods

GUSTO Trial Design

The trial design and primary outcome results of the GUSTO trial have recently been published.²² In this trial over 41,000 patients were randomized to

one of four treatment groups containing streptokinase, tPA, or a combination of the two, with 30-day mortality assessed as the primary endpoint. Within the GUSTO trial, a substudy was conducted with over 2,000 patients undergoing acute catheterization at 90 minutes, 3 hours, 24 hours, or 7 days to angiographically define infarct artery patency. Left ventricular function in these patients was also measured.

The electrocardiographic-monitoring substudy was conducted largely within the angiographic substudy. The purposes of the substudy were threefold: (1) to profile the speed of ST-segment recovery across drug regimens, (2) to profile the stability of ST-segment recovery across drug regimens, and (3) to compare noninvasive patency assessment, based on continuous ST-segment recovery analysis, with simultaneous angiographic patency.

Population

The population treated in the GUSTO trial were age-unrestricted patients presenting with chest pain of less than 6 hours continuous duration and persis-

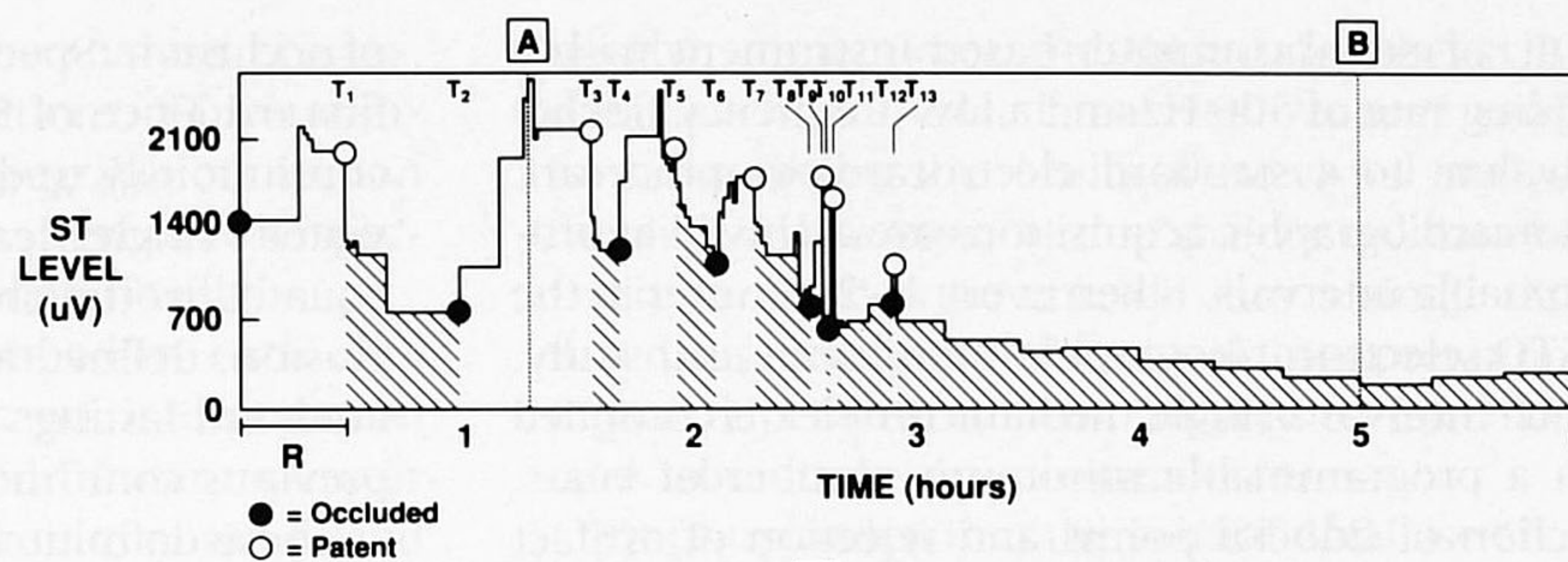
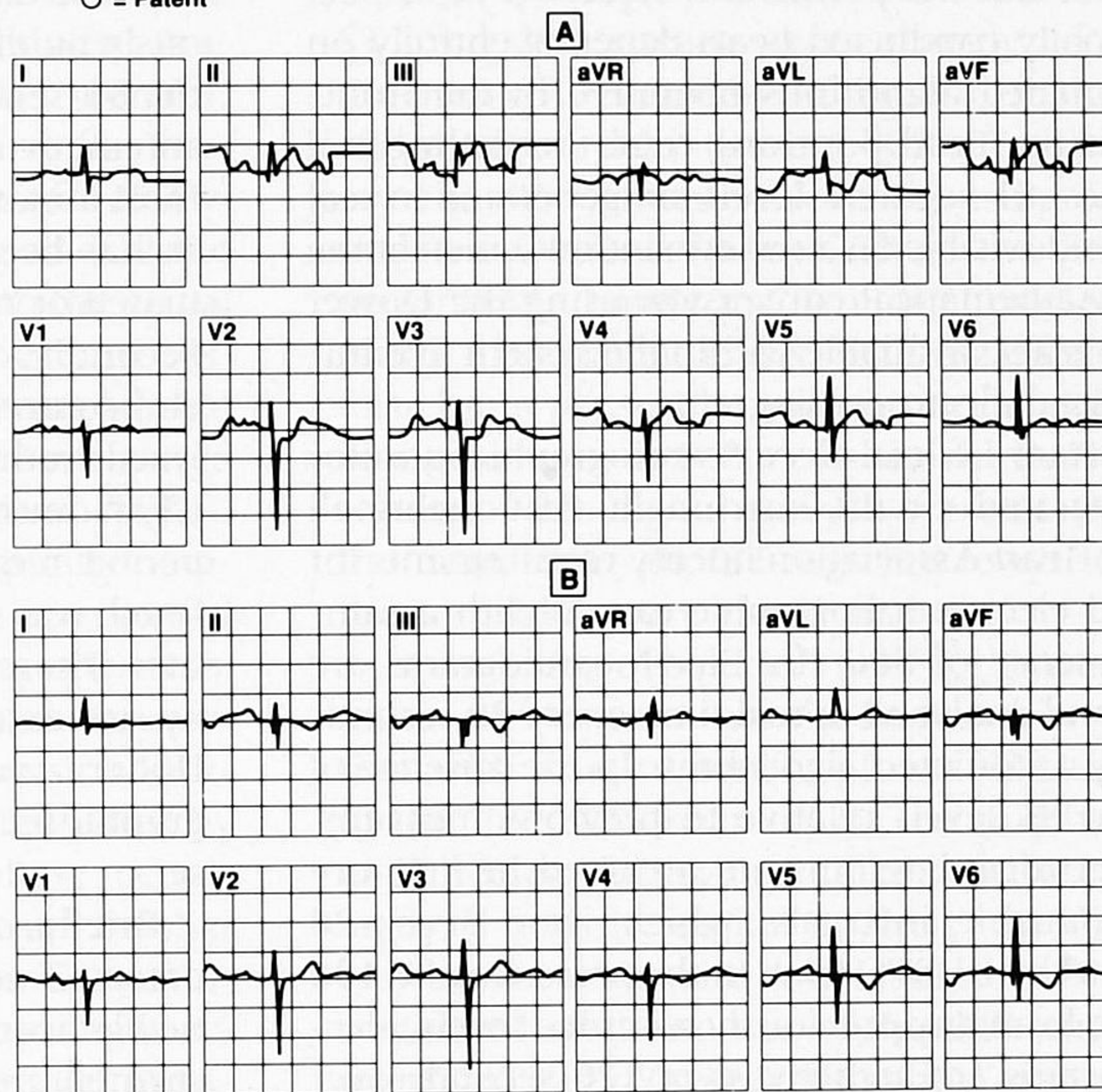


Fig. 1. (Continued) (C) Two-dimensional trend of ST level over time, showing criteria-based transitions from occluded (white intervals under trend) to patent (shaded intervals under trend) or vice versa. Representative analog waveforms at peak (A) and baseline (B) are shown below trend. All visual analysis modalities in the GUSTO electrocardiographic-monitoring substudy involve a human operator that directly examines analog waveforms in conjunction with digital trend displays. Modified from Krucoff MW, Croll MA, Pope JE.¹⁶ With permission.



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tent ST-segment deviation diagnostic of myocardial infarction. Patients were evenly randomized across four drug regimens: (1) streptokinase with intravenous heparin, (2) streptokinase with subcutaneous heparin, (3) front-loaded tPA with intravenous heparin, and (4) combination streptokinase and tPA with heparin. All patients received aspirin.

At the sites participating in the electrocardiographic-monitoring substudy, all patients enrolled in the main trial were considered eligible for the substudy.

ST-Segment Monitoring

ST-segment monitoring was targeted to begin at or prior to the onset of thrombolytic therapy and continue for a minimum of 18 hours. One of three devices was used in each patient: a three-channel Holter (Marquette Electronics, Milwaukee, WI), a

three-channel continuous vectorcardiographic monitor (MIDA 1000, Ortivus Medical, Stockholm), or a 12-lead continuous electrocardiographic monitor (ST-100, Mortara Instrument, Milwaukee, WI).

The Holter recorder is an amplitude-modulated, magnetic tape-based, four-channel recorder that uses three channels for an analog electrocardiographic signal and the fourth channel for a digital timing track. Positions for the three bipolar leads were selected from previous studies^{10,23} to support the most robust interrogation of injury current from coronary occlusion over the precordium. All data were archived on magnetic tape on the front-end recorder. Fiducial point measurements, artifact, and arrhythmia editing are all functions of playback analysis (Marquette 8000 Holter scanner). Over the entire record-playback loop the sampling rate is 125 Hz, with a frequency response fidelity to about 0.05 Hz. ST-segment information from the Holter monitor was available only retrospectively.

The vectorcardiographic monitor is an integrated

circuit, personal computer-based instrument with a sampling rate of 500 Hz and a low-frequency fidelity equivalent to a standard electrocardiographic cart. Vectorcardiographic acquisitions are archived at programmable intervals, taken every 1–2 minutes in the GUSTO electrocardiographic-monitoring substudy. In each interval a single median complex is compiled from a programmable minimum number of beats. Selection of fiducial points and rejection of artifact or abnormally conducted beats depends entirely on fully automated algorithms operative in the front-end recording. Lead positions were the orthogonal XYZ bipoles. ST-segment levels are generated in real time as trends visible on a review station screen at the bedside. Mathematical conversion using the Dower transform is also available within the system to emulate a 12-lead electrocardiogram.

The Mortara 12-lead electrocardiographic monitor is an integrated circuit instrument that meets all American Heart Association fidelity requirements for a standard electrocardiographic cart,²⁴ with a sampling frequency of 500 Hz. Electrocardiograms are acquired and analyzed in real time every 20 seconds using fully automated algorithms. In the absence of changes in ST levels relative to previous measurements, electrocardiograms are archived in memory at programmable intervals, which were every 20 minutes for the GUSTO trial. In the presence of >100 μV change from any previously recorded levels, electrocardiograms are archived every 20 seconds over a period of 3 minutes. Selection of fiducial points and rejection of noisy electrocardiographic signals are accomplished in real time and are dependent on fully automated algorithms. There is no automated arrhythmia rejection in the front-end recording. The usual 10 electrodes (9 primary leads and 1 ground lead) are applied to generate the 12-lead electrocardiographic. For the GUSTO trial, electrodes on the limbs were applied in torso positions to ensure signal stability over the course of monitoring. ST-segment levels were generated in real time as trends accessible on the bedside instrument.

ST-Segment Analysis

The goal of ST-segment analysis was to provide a quantitative emulation of physiologic recovery directly related to the ongoing status of infarct artery patency. The method adopted involved modifications of the continuously updated ST-segment recovery analysis technique.^{16,17} The two primary end-point measurements were selected to independently reflect speed of reperfusion and timing and incidence

of occlusion. Speed of reperfusion was equated to the first evidence of 50% recovery from the preceeding, continuously updated peak ST level in the most deviated single lead. Stability of reperfusion was equated to the absence of episodes suggesting reocclusion, defined as ST reelevation in the single lead analyzed lasting >60 seconds of >100 μV from the previous continuously updated baseline level.

These definitions represent modifications of previously published work¹⁶ in two particular areas. First, the ST-segment trend of level over time, or the measurement matrix, was always taken as the single most abnormal lead, rather than the sum of all leads, as has been used previously if the peak lead fluctuated or multiple precordial zones were active.^{16,17} Secondly, ST reelevation from updated baseline levels required only >100 μV in the single lead analyzed, rather than >150 μV in two leads or >200 μV in one lead used in previous studies.^{16,17} The time period requirement, in which reelevation was defined, was shortened from <60 minutes to <10 minutes. These modifications were incorporated primarily to accommodate the combined utilization of Holter, vectorcardiographic, and electrocardiographic recordings and analyses in a single, final data set.

Briefly, as illustrated in Figure 1, continuously updated ST-segment recovery analysis references each newly acquired ST-segment level to all previous ST-segment measurements from the same patient in the same lead. Each newly acquired ST level is thus characterized as improving or worsening over time. If a patient's ST levels change from worsening to improving, or vice versa, this change creates a transition peak or a trough in the trend of ST-segment level versus time (Fig. 1). For interpretative purposes, each newly acquired ST-segment level can be quantitatively related to the immediately preceding transition point.

Visual and Digital Analysis of ST Recordings in the GUSTO Trial

Three core laboratories were organized to independently analyze studies recorded with each of the three devices. All Holter data were processed by the Holter monitoring core laboratory in Toronto, all vectorcardiographic data were processed by the vectorcardiographic monitoring core laboratory in Rotterdam, and all electrocardiographic data were processed by the electrocardiographic monitoring core laboratory in Durham, North Carolina. All core laboratories were kept blinded to drug treatment and an-

giographic patency throughout the analysis process. For simultaneous patency correlations, ST trend information subsequent to the angiographic injection itself was also blinded in order to prevent retrospective bias, as has previously been described.¹⁷

Visual analysis was first performed in each core laboratory, where both editing and interpretation was performed by an experienced human operator using a computer-assisted device to observe and measure actual waveforms. Holter studies were analyzed on the Marquette 8000 Laser Holter monitor. The front end of this playback unit digitizes the analog signal from tape at a sampling rate of 125 Hz, identifying fiducial points and classifying all detected beats using automated algorithms prior to the visual reading by a human operator. After all beats are visually confirmed, ST-segment levels on beats labeled as normal conduction and low noise are measured using incremental averaging over 15 second epochs.

Vectorcardiographic studies were visually analyzed within the MIDA 1000 monitor augmented using Coronet bedside monitoring software (Ortivus, Sweden) and additional custom-made software developed in Rotterdam. Beats defined as noisy, abnormal conduction, or other arrhythmias eliminated by automated "intelligence" during acute phase recording do not appear in the information stream. Further editing or deletion of the noisy or abnormally conducted beats that are archived in the recording is accomplished manually. ST-segment levels are measured instantaneously (ie, with no incremental criteria) for each existing waveform left resident in the data stream.

Electrocardiographic studies were visually analyzed on the custom-written workstation environment standard to the Duke ischemia monitoring laboratory, as has previously been described.^{11,16,17} Electrocardiographic acquisitions determined as "no change" during real-time recording do not appear in the information stream other than at the mandatory period every 20 minutes. Further editing or deletion of noisy or abnormally conducted waveforms that are archived in the recording is accomplished manually. ST-segment levels are measured instantaneously for each existing waveform left resident in the data stream.

Using continuously updated methods within the architecture of the scanning environment for each genre of recording, the time of the first 50% recovery and the onset and offset of any episodes of ST relevation were recorded. Once the study was edited and a visual interpretation completed, all measurements of ST-segment levels were downloaded from the playback system as a digital data stream onto floppy disks, including patient identifiers (name, study

number, time, date) and time-date labeled ST-segment levels for the lead analyzed. A paper transmittal form containing the results of the visual analysis and the digital data were sent to the central data bank in Durham. Both were entered into a single database that thus combined the visual interpretations and digital data streams from all studies from all three core laboratories in a common format.

Once uploaded into the central database all digital ST level data streams were reanalyzed by an SAS program written precisely according to the amplitude and duration definitions of 50% ST-segment recovery and ST-segment relevation using continuously updated reference points. Thus, the SAS program performed a purely mathematical or digital analysis of the ST-segment levels, with no human or waveform input per se. The graphic output of this program was generated in S-Plus, as shown in Figure 2. The results of this digital analysis were matched against the time, date, and ST-segment levels logged in by the core laboratory visual analysis.

In the event of a perfect match, the study interpretation was entered into the final data set for correlation with drug-treatment groups. If either the time to the first 50% recovery or the number or timing of ST relevation events differed between the visual analysis and the digital analysis, the disparity was conveyed back to the core laboratory from which it originated so the source of the differences could be identified based on reexamination of the original recording.

Combined ST-Segment Recording Study

The final data set for the GUSTO electrocardiographic-monitoring substudy incorporated streams of ST-segment measurements from three record/playback systems with many similarities and fundamental differences, including sampling rates, archiving strategies, noise and signal management, lead positions, arrhythmia detection, fiducial point identification, and analysis environments, among others. To better define the potential impact of these differences on analyses, like the planned GUSTO trial endpoints, 60 elective angioplasty patients were hooked up to all three ST monitoring devices simultaneously during balloon occlusion in each of the three major epicardial arteries. In these studies two kinds of parameters were assessed. ST-segment amplitudes, as absolute values, were assessed both at baseline prior to balloon inflation and at the moment of peak ischemia, just prior to balloon deflation. Internally referenced parameters, such as the percent recovery from peak changes and the time from peak to 50% recovery were also measured.

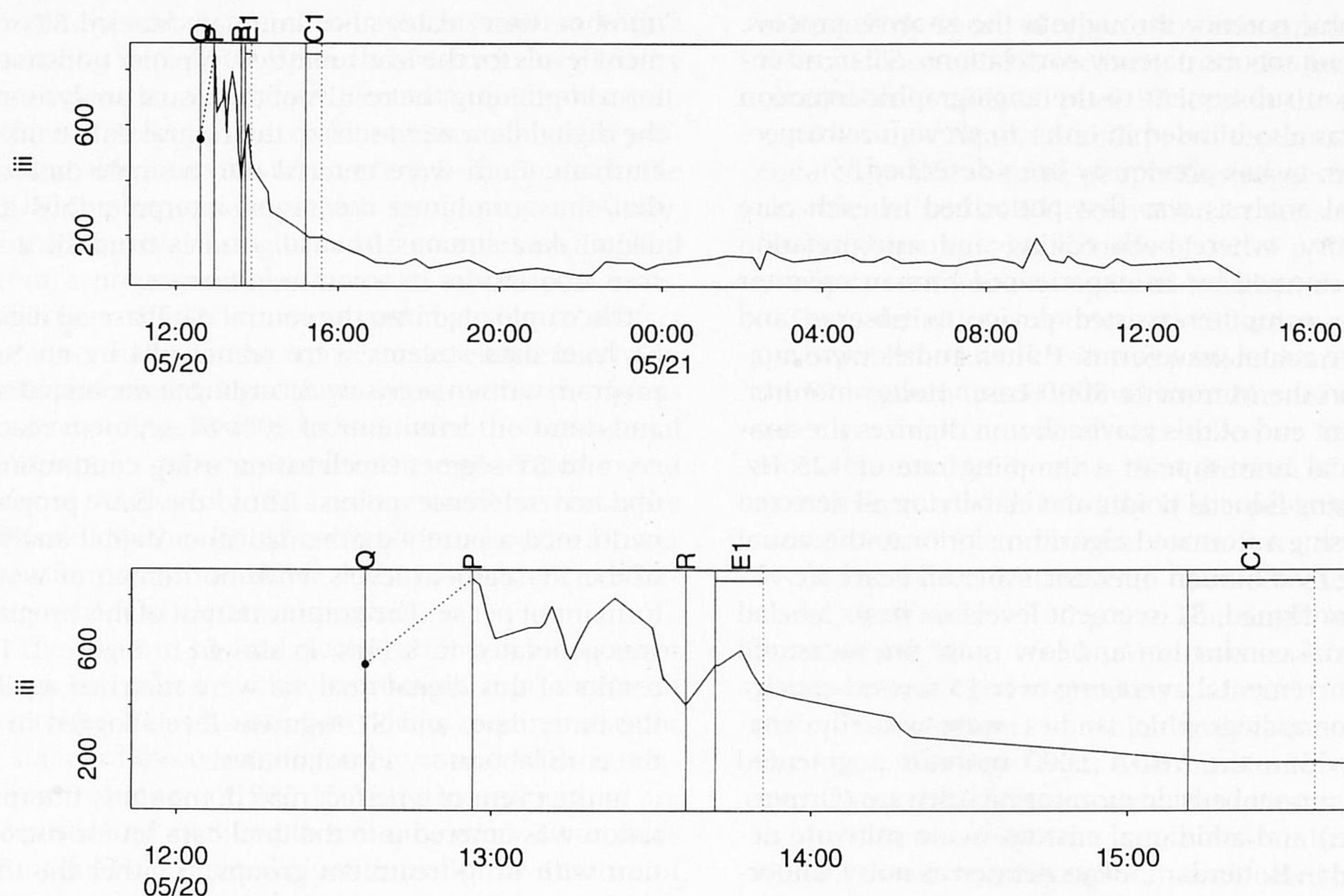


Fig. 2. Single most active lead trend from a single patient with inferior infarction; S-Plus output for GUSTO electrocardiographic substudy quality control. Key points (Q = qualifying electrocardiographic ST level; P = peak ST level; R = first evidence of 50% recovery from peak ST level; E1 = first reelevation event; C1 = period of acute catheterization) are selected and displayed based solely on clock times or on numeric calculation using the study criteria, with no human input or waveform visualization. Upper and lower panels: study no. 446-020; start time, 5/25/92 12:56:15.

Discussion

The structural design of the GUSTO electrocardiographic-monitoring substudy integrates a number of clinical and technical investigational directions. The primary hypothesis is the focus on the comparison of drug-treatment strategies using different thrombolytic regimens in patients suffering acute infarction. Quantitatively analyzed, continuous ST-segment recovery analysis is applied as an endpoint marker of the speed and stability of drug efficacy. Independent of treatment group, this substudy also seeks to better characterize the relationship between reperfusion and outcomes variables, such as left ventricular function and mortality. Integrated largely into the angiographic substudy in GUSTO, our investigation has the potential to provide a continuous context (quantitative ST-segment recovery over time) in which the angiographic patency snapshot might be interpreted. This relationship might help to better clarify some of the controversies still surrounding the place of static anatomic definition and the continuous or ongoing pathophysiology of infarction.

The technical dimensions of the GUSTO electrocardiographic-monitoring substudy are at least as large as the clinical investigations. Continuous ST-segment recovery analysis has previously been proposed as a synthesis of the amplitude, duration, and precordial geography of ST-segment activity defined by serial multilead recordings.^{16,18} In the GUSTO substudy the use of three discrete devices (Holter, vectorcardiographic and electrocardiographic) mandated the modification or elimination of a number of ST recovery criteria. The ability to weld a single data set from three core laboratories using three discrete devices and still retain sufficient information to address the important clinical investigational questions is a major challenge for this trial.

To assist in the appreciation of how strongly the similarities and differences between the devices per se were likely to influence interpretation of ST-segment behavior, the combined ST-segment project was designed to compare all three devices recording a single series of coronary occlusion/reperfusion events analyzed in a single core laboratory. The parameters selected for the combined ST-segment analysis should give information about the effects of lead po-

sition, signal processing, and basic measurement, although will add little insight into noise and artifact management. Parameters were selected to test device-related variances in end-analysis ST-segment deviation amplitudes and time-related recovery.

As a final measure of technical consistency, the influence of direct visualization of the recorded waveform by a human being will be measured, as a quality control device, by an SAS-based automated program that runs the mathematical definitions for ST recovery and ST reelevation on the digital streams of ST levels. This quality control measure may afford considerable insight into the vicissitudes of implementation of our study findings into future ST device architectures.

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