ST Variability during the First 4 Hours of Acute Myocardial Infarction Predicts 1-Year Mortality

Per Johanson, M.D., Karl Swedberg, M.D., Ph.D.,
and Mikael Dellborg, M.D., Ph.D.

From the Clinical Experimental Research Laboratory, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Background: Early and complete myocardial reperfusion is the goal when treating a patient with acute myocardial infarction. To achieve this in each individual, an on-line, accurate, easily handled and preferably noninvasive technique to monitor flow alterations is needed. Recurrent ST-segment elevation has been shown to reflect cyclic disturbances in perfusion.

Methods: We have retrospectively analyzed ST variability in 102 patients with acute myocardial infarction randomized to 100 mg of rt-Pa or placebo. Patients were monitored for 24 hours using vectorcardiography.

Results: Patients alive at one year (86%) had significantly less ST variability during the first four hours: 4.3 versus 7.1 episodes, $P = 0.007$. Patients having six or more ST episodes showed a 31.3% one-year mortality as compared to no mortality in patients having no ST variability. Furthermore ST variability was reduced by fibrinolysis.

Conclusion: Early ST variability detectable in real time is associated with worse outcome.

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Acute myocardial infarction usually results from an occluded coronary artery.¹ The ultimate goal in acute treatment of myocardial infarction during the last decades has been to reperfuse the occluded artery by fibrinolysis or angioplasty, restore circulation to the myocardium at risk, and thereby achieve a more favourable outcome for the patient.^{2–6} Coronary angiograms have been suggested to be the gold standard to predict prognosis in coronary artery disease^{7,8} and estimating success-rate after fibrinolysis.⁹ However this method can only demonstrate a snapshot¹⁰ of a dynamic process^{11–13} in the epicardial circulation. Furthermore it gives limited information about the circulation at the microvascular level.^{14,15}

ECG development during infarction has been shown to be of prognostic value. Resolution of ST segment elevation (ST recovery), has been shown

to predict both patency^{16–18} and prognosis^{19–23} in patients with AMI. This parameter is superior as compared to the angiogram, in predicting outcome after successful primary angioplasty,²⁴ and successful fibrinolysis.²⁵ Continuous ST monitoring provides real-time presentation of the dynamic variations in ECG changes, and has been shown to be superior to single-ECGs recorded sequentially in acute coronary syndromes.²⁶

By continuous ECG monitoring, we can survey even very short-lasting episodes of ST segment deviation (ST variability). This variability has been shown to correlate with a cyclic flow in the infarct related artery,¹² to be associated with an unstable clinical situation and higher enzymatic maxima,²⁷ and to predict reocclusion,²⁸ despite conventional ECG signs expressing reperfusion.²⁹

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Address for reprints: Dr. P. Johanson, Clinical Experimental Research Laboratory, Sahlgrenska University, Hospital/Östra, SE-416 85 Göteborg, Sweden. Fax: +46 31 19 14 16; E-mail: pj@hjl.gu.se

We wanted to test an algorithm for significant early ST variability in this population of patients with ST elevation infarctions, and to evaluate if this parameter contained prognostic information. In this study, performed just prior to the end of placebo controlled trials in reperfusion for myocardial infarction, modern ECG techniques were used, giving us a unique possibility to analyze cyclic variations of the ST segment in patients treated with placebo.

METHODS

Three hundred fifty-two patients were included in the TEAHAT-study,³⁰ a comparison between very early treatment with t-PA and placebo, performed between 1986 and 1988. Inclusion criteria were chest pain and strong suspicion of acute myocardial infarction for more than 15 minutes but less than 2 hours and 45 minutes, and age below 75 years. Exclusion criteria were increased risk of bleeding due to hemorrhagic diathesis, gastrointestinal or urogenital bleeding, or treatment with anticoagulants, a history of recent (within 6 months) stroke, uncontrolled hypertension (diastolic blood pressure > 120 mmHg), diabetic retinopathy, severe liver or kidney disease, major trauma (within 6 months), childbearing capacity, and suspected aortic dissection.

One hundred and seventy-eight of these patients with suspected acute myocardial infarction were included in the vectorcardiographic substudy³¹ on an availability basis. All patients received intravenous heparin and were randomized to either 100 mg of rt-PA over 3 hours or placebo. Aspirin and beta-blockers were administered unless contraindicated. Patients were monitored for at least 24 hours after admission using the MIDA system for vectorcardiography (VCG), previously described in detail.²⁷ Concisely, eight electrodes are placed according to Frank,³² resulting in three orthogonal leads X, Y, and Z, that are continuously monitored and analyzed. After the operator accepts a template QRS complex for that patient, the computer automatically discards all QRS complexes with grossly altered configuration and thereby hinders, for example, ventricular extrasystoles and sequences of rapid intraventricular rhythm from disturbing the analysis. The beats are averaged over 2 minutes. Both ST and QRS parameters were monitored and recorded. ST vectormagnitude (ST-VM) was calculated from the orthogonal leads according to the

formula: $ST - VM = \sqrt{X_i^2 + Y_i^2 + Z_i^2}$, representing the total, spatial ST-segment shift from the baseline, where X_i is the magnitude of ST deviation in lead X, 20 ms after the J-point. Changes in the ST-VM were calculated and presented as a trend curve. All calculations of trend curve parameters were done online.

Initial and maximal ST-VM were recorded. Time to ST decline, i.e., time to ST resolution to a stable (30 minutes or more) baseline was calculated (Fig. 1).

ST variability was analyzed during the first 4 hours of observation only. This arbitrary cut-off has been used for describing early ST variability,^{27,31} and represents the time-point when 75% of patients in this population had reached a stable baseline in ST-VM. Episodes of ST-segment variability with an increase in ST-VM exceeding 25 μV , for more than 2 minutes were considered significant. The number of such episodes was counted. Changes in the QRS-Vector difference (QRS-VD),²⁷ a vectorcardiographic parameter reflecting changes in the shape of the QRS complex, were also analyzed. The mean value of QRS-VD between 20 and 24 hours of observation was registered (Fig 1). Analyses were made by two blinded and independent observers.

The present analysis is based on all patients with confirmed AMI who underwent continuous ST monitoring (n = 102). The follow-up period was 1 year.

Statistical Analysis

Categorical background data were compared at baseline by the chi-square test. Logistic regression and multiple logistic regression were used to deter-

Figure 1. Schematic trend-curves of ST-vector magnitude (ST-VM) and QRS-vector difference (QRS-VD) during an acute myocardial infarction. A = Initial ST-VM; B = Maximal ST-VM; C = Time to ST-decline; D = ST-variability; E = QRS-VD at 20 to 24 hours.

Table 1. Baseline Characteristics

	rt-PA n = 52	Placebo n = 47	P
Age, mean, years	61.3	61.4	0,95
Previous myocardial infarction, %	32	33	0,94
Hypertension, %	21	21	0,96
Diabetes, %	9.6	2.1	0,21
Hyperlipidemia, %	13.5	10.4	0,64
Previous angina, %	40	50	0,33

mine the independent effects of different vectorcardiographic parameters on one-year mortality. $P < 0.05$ was considered significant.

RESULTS

One hundred and two patients with AMI were included. One patient was excluded due to lack of 1-year information, two patients due to lack of sufficient VCG-data, leaving a total of 99 patients for analysis. For baseline characteristics see Table 1.

Patients alive at 1 year (86%) had significantly less ST variability, lower maximal and initial ST-VM, and lower QRS-VD at 20 to 24 hours of observation (Table 2). In a multivariate analysis, only QRS-VD at 20 to 24 hours ($P = 0.019$) and ST variability ($P = 0.047$) contributed to information about prognosis (Table 3).

The median number of ST variability episodes was four. Patients having four or more episodes had a 22.2% 1-year mortality as compared 4.4% in those with less than four episodes ($P = 0.01$). This gives a sensitivity of 85% and negative predictive value of 96%. Patients with four or more episodes of ST variability showed significantly longer delay

Table 2. Univariate Analysis of Vectorcardiographic Parameters

	Alive at 1 year		P
	No n = 14	Yes n = 85	
Maximal ST-VM*, μ V	424	255	0.0018
Number of ST-VM* episodes	7.1	4.3	0.007
Initial ST-VM*, μ V	307	199	0.023
Time to ST-decline, min	211	184	0,64
QRS-VD† 20–24h, μ Vs	46	28.2	0.003

* = ST-vectormagnitude; † = QRS-vectordifference.

Table 3. Multivariate Analysis of Vectorcardiographic Parameters: Relative Risk for 1-Year Mortality

	RR	95% CI	P
Number of ST-VM* episodes	1.22	(1.01–1.50)	0.047
QRS-VD† 20–24h, μ Vs	1.06	(1.01–1.11)	0.019
Initial ST-VM*	1.0	(0.99–1.01)	0,78
Maximal ST-VM*	1.0	(0.99–1.01)	0,79

* = ST-vectormagnitude; † = QRS-vectordifference.

to ST decline to a stable value, 229 minutes, as compared to those with less than four episodes, 110 minutes ($P = 0.003$).

When grouping the patients according to number of significant episodes of ST variability, patients with six or more episodes showed a 31.3% 1-year mortality compared to no mortality at all in the group with no ST variability (Fig. 2).

Patients receiving t-PA showed fewer ST episodes, shorter time to ST decline to a stable baseline, lower QRS-VD at 20 to 24 hours, and shorter time to reaching a stable QRS-VD plateau (Table 4).

In the placebo group ($n = 47$) 1-year overall mortality was 17% with a 22.6% mortality (7 of 31 patients) for those with four variability episodes or more, as compared to 6% (1 of 16) in patients having less than four episodes ($P = n.s$). Patients receiving t-PA showed a trend towards lower 1-year mortality, 12 versus 17% ($P = n.s$). This trend was consistent independently of what grade of ST variability the patients showed.

DISCUSSION

This study suggests that continuous vectorcardiography during acute myocardial infarction is

Figure 2. One-year mortality (%) by ST variability during the first 4 hours of observation.

Table 4. Influence of rt-PA on Vectorcardiographic Parameters

	rt-PA n = 52	Placebo n = 47	P
Number of ST episodes	3.9	5.7	0.015
Time to ST-decline, min	157	220	0.033
QRS-VD† 20–24h, μ Vs	25.8	34.7	0.011
Time to QRS-plateau, min	178	303	0.004

† = QRS-vectordifference.

useful in identifying high-risk patients at a very early stage of their disease. ST variability, according to the algorithm introduced, predicted long-term survival-rate after only 4 hours of observation and treatment.

Recurrence of intermittent ST elevation has been shown to reflect temporary closure of the coronary artery afflicted in serial angiograms,¹² and has been suggested to presage reocclusion.²⁸ Cyclic coronary flow during infusion of t-PA has been shown to precede reocclusion of the infarct related artery.¹³ However, a single early coronary angiogram does not give enough information for accurate risk-stratification. Despite quantitative and morphologic analyses of the 90-minute angiogram this does not predict recurrent ischemic events.³³ 90-minute patency has been said to be an illusion of optimal reperfusion. Where one has anticipated that, in a population showing an 85% 90 minutes patency, only 25% experience a rapid, complete, and sustained restoration of myocardial perfusion.¹⁰

Thus, in the light of previous evidence, the pattern of recurrent ST variability may be connected to a nonsustained myocardial (re-)perfusion in patients with acute myocardial infarction. An increased ST variability seems to be a malignant phenomenon. This might reflect different prerequisites in ability to lyse a thrombus with or without exogenous fibrinolytic treatment. A common genetic variation at the t-PA locus has already been shown to correlate to interindividual differences in release rates of t-PA.³⁴

A small trial of 57 patients with acute myocardial infarction showed that patients with a spontaneous ST variability, prior to giving the fibrinolytic drug had higher thrombogenic activity and lower t-PA antigen levels.³⁵ In contradiction to our findings, spontaneous variability also seemed to have a protective effect.

In the present study, treatment with t-PA, as compared to placebo, lowered mortality in a similar magnitude to what has been shown in larger studies.^{2,3} Fibrinolytic treatment also significantly reduced intermittent disturbances in reperfusion, expressed by less ST variability and, as previously presented³¹ and thereby not further discussed here, enhanced ST decline, and reduced QRS-VD. The placebo group, in which variability was "spontaneous" and not influenced by fibrinolysis, showed although not significantly, a difference in outcome consistent with results in the total material.

Recent and coming trials of acute ST elevation infarction focuses on new points of attack to enhance fibrinolytic therapy, lyse a thrombus, and achieve reperfusion. Antiplatelet agents such as GP IIb/IIIa inhibitors may further reduce ST variability and cyclic disturbances in reperfusion.

Despite the fact that this is a retrospective study of a limited population, we believe the finding that even small variations in the ST segment early after onset of acute myocardial infarction are of interest as a marker of prognosis. Further evidence will be collected.

CONCLUSION

ST variability during the first hours of acute myocardial infarction is associated to worse outcome and can be detected noninvasively, on-line with continuous ECG surveillance. It may represent a nonsustained myocardial (re-)perfusion. Fibrinolytic treatment in combination with heparin reduces these variations.

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