

Association of the timing of ST-segment resolution with TIMI myocardial perfusion grade in acute myocardial infarction

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Background More complete ST-segment resolution (ST res) in acute myocardial infarction (MI) has been associated with better epicardial and myocardial reperfusion as assessed with the Thrombolysis in Myocardial Infarction (TIMI) flow grade (TFG) and the TIMI myocardial perfusion grade (TMPG), respectively. However, no data exist comparing the speed of ST resolution on continuous electrocardiogram (ECG) monitoring with the TMPG on coronary angiography. We hypothesized that delayed ST res is associated with impaired TMPGs.

Methods Continuous 12-lead ECG recordings and 60-minute angiographic data were analyzed in 120 patients with acute MI who received tenecteplase monotherapy or combination therapy with low-dose tenecteplase and eptifibatid in the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) trial.

Results More rapid ST res on continuous ECG monitoring was associated with improved TMPGs on coronary angiography performed 60 minutes after study drug administration. For TMPG 3, the median time to ST resolution was 53 minutes. For TMPG 2, 1, and 0, the corresponding times were 64 minutes, 80 minutes, and 106 minutes, respectively ($P = .01$ for trend). Likewise, more rapid ST res was also associated with faster epicardial flow. For TFG 3, the median time to ST resolution was 46 minutes, compared with 109 minutes for TIMI flow grades 0 to 2 ($P = .001$). The corresponding times for a corrected TIMI frame count ≤ 40 versus > 40 were 52 minutes and 112 minutes, respectively ($P < .001$).

Conclusions Although the static ECG has been associated with epicardial and myocardial blood flow in the past, this study extends these observations to demonstrate that more rapid ST res on continuous ECG monitoring is associated with improved myocardial perfusion after thrombolytic administration. (*Am Heart J* 2004;147:847–52.)

To advance the growing field of device studies in ST elevation myocardial infarction (MI), valid surrogate biomarkers are needed because multiple large-scale mortality trials are not likely given cost constraints. One measure of successful reperfusion after fibrinolytic administration is the extent of ST-segment resolution on the static 12-lead electrocardiogram (ECG).¹ Greater ST resolution on the static ECG has been re-

lated to smaller subsequent infarct size, improved infarct zone wall motion,^{2,3} and improved survival rate.^{4,5} Likewise, studies of continuous ECG monitoring have associated faster and more complete ST resolution with better clinical outcome^{6,7} and a greater likelihood of infarct-related artery patency and blood flow, as assessed with Thrombolysis in Myocardial Infarction (TIMI) flow grade (TFG).^{8,9} Furthermore, greater ST resolution on a static ECG has been related to improved myocardial reperfusion as assessed with the TIMI myocardial perfusion grade (TMPG).^{10,11} Although static ECG studies have been used to demonstrate the importance of the magnitude of ST resolution, little data exist comparing the speed of ST resolution on continuous ECG monitoring with myocardial perfusion on the angiogram. We hypothesized that delayed ST resolution on continuous ST segment monitoring would be associated with impaired TMPGs on coronary angiography.

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Table I. Baseline characteristics

Variable	Time to ST res (min)	No.	P
Age (y)			
≥ 65	59 (11, 111)	42	
< 65	63.5 (8, 108)	78	.84
Sex			
Male	71 (22, 119)	91	
Female	21 (0, 70)	29	.013
Race			
White	64 (21, 109)	93	
Nonwhite	58 (0, 121)	27	.61
Hx HTN			
Yes	47.5 (0, 124.5)	36	
No	65 (21, 108.5)	84	.52
Hx HC			
Yes	24 (5, 62)	33	
No	74 (16, 120.6)	87	.02
Hx DM			
Yes	52 (0, 146)	21	
No	64 (20, 109)	99	.69
Hx MI			
Yes	52.7 (11, 109)	18	
No	63.5 (8, 111)	102	.78
Hx CHF			
Yes	66 (21, 90)	3	
No	62 (8, 111)	117	.93
TOB			
Yes	64 (21, 108)	53	
No	60 (0, 111)	67	.68

Values are reported as median (25th percentile, 75th percentile). *ST res*, ST resolution; *HTN*, hypertension; *HC*, hypercholesterolemia; *DM*, diabetes mellitus; *MI*, myocardial infarction; *CHF*, congestive heart failure; *TOB*, current tobacco smoker.

Methods

The Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) trial randomized 418 patients with acute MI prospectively to receive a combination of eptifibatid and reduced-dose tenecteplase (TNK) or full-dose TNK.¹² Continuous 12-lead ECG monitoring was performed as a substudy of the larger trial involving 32 hospitals in the United States. Angiographic and ECG analyses were performed at 2 separate core laboratories, and data were available from both laboratories in 120 patients. All patients underwent angiography 60 minutes after study drug administration and had TFG, TMPG, and corrected TIMI frame counts (CTFC) assessed, as described previously.¹³⁻¹⁵ In brief, in TMPG 0, there is minimal or no myocardial blush; in TMPG 1, dye stains the myocardium, and this stain persists on the next injection; in TMPG 2, dye enters the myocardium but washes out slowly so that the dye is strongly persistent at the end of the injection; and in TMPG 3, there is normal entrance and exit of dye in the myocardium. The TMPG was able to be evaluated in 118 patients.

All patients underwent continuous 12-lead ECG monitoring with the RZ-153 digital 12-lead Holter (Northeast Monitoring, Boston, Mass). These devices acquire and archive a standard 12-lead ECG every 60 seconds and a continuous 3-lead rhythm strip. Monitoring was initiated at the time of study

enrollment and continued 24 hours. The ECG data were analyzed in a blinded manner in the Ischemia Monitoring ECG Core Laboratory (IML) at the Duke Clinical Research Institute (Durham, NC). Detailed definitions of IML standard parameters of ST-segment recovery analysis have been published previously.¹⁶ The time to ST resolution was defined as the time from the initiation of drug infusion to the onset of stable ST-segment recovery. Onset of stable ST recovery is defined as the beginning of a period of $>50\%$ recovery from previous peak ST levels in the most deviated lead, lasting >4 hours, without further ST evolution ($>100 \mu\text{V}$).¹⁶ The area under the curve (AUC) was defined as the area under the ST-deviation versus time-trend curve from the onset of study drug administration through the subsequent 3 hours, reported as $\mu\text{V}\cdot\text{minutes}$. ST-segment resolution was also analyzed at 30 minutes and at 60 minutes, and complete resolution was defined as $\geq 70\%$ recovery from previous peak ST levels in the most deviated lead.

Statistical analysis

Variables were compared with the Fisher exact test or the χ^2 test for categorical data. The Student *t* test was used for the analysis of normally distributed continuous variables. The nonparametric Wilcoxon rank sum test (for 2-way comparisons) or the Kruskal-Wallis test (for 3-way comparisons) was used to compare continuous variables when the data were not normally distributed or when the data were imputed to an occluded vessel. To assess the association of both the percent ST resolution on the basis of static ECG and the time-to-resolution on the basis of continuous ST-segment monitoring with angiographic end points (TFG and TMPG), both ST variables were entered into a multivariate logistic regression model (both as continuous variables and not as categorical variables to achieve better statistical parity in the relative power of the 2 variables).

Results

Angiographic and electrocardiographic data were both available for 120 patients. The TMPG was not able to be evaluated in 2 patients. Hypercholesterolemia and female sex were associated with more rapid ST resolution (Table D). Baseline characteristics were similar between the patients in this substudy and patients who were not included in the substudy, with the exception of white race and history of hyperlipidemia (77.5% vs 92.6%, $P < .001$; and 27.5% vs 18.5%, $P = .04$, respectively; Table II).

Impaired TMPGs on the 60-minute angiogram were associated with delayed ST resolution (Figures 1 and 2). For TMPG 3, the median time to complete stable ST resolution was 53 minutes (25th percentile, 8 minutes; 75th percentile 95 minutes; $n = 68$). TMPG 2 was present in only 1 patient, and in that patient, ST resolution occurred at 64 minutes. For TMPG 1, the median time to ST resolution was 80 minutes (8-123 minutes; $n = 19$), and for TMPG 0, ST resolution occurred at 106 minutes (44-140 minutes; $n = 30$; 4-way $P = .01$).

Table II. Baseline characteristics by participation in continuous ST resolution substudy

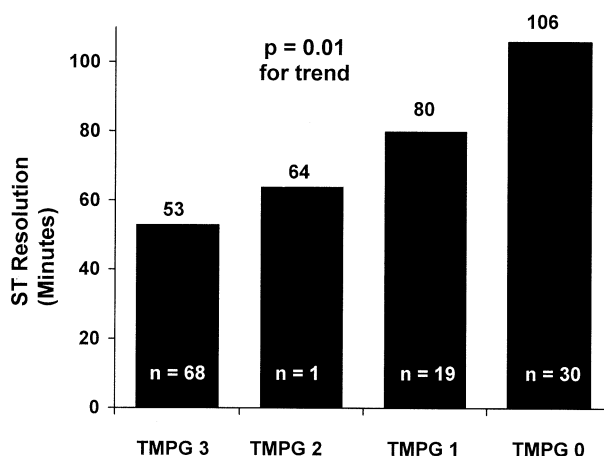
	Participant in substudy (n = 120)	Not in substudy (n = 298)	P
Age ≥65 y (%)	35.0	29.9	NS
Sex (% male)	75.8	76.9	NS
Race (% white)	77.5	92.6	<.001
Hx hypertension (%)	30.0	36.6	NS
Hx hypercholesterolemia (%)	27.5	18.5	.040
Hx diabetes (%)	17.5	13.1	NS
Prior MI (%)	15.0	12.1	NS
Hx CHF (%)	2.5	1.3	NS
Smoker (%)	44.2	49.3	NS

Complete ST resolution was present at 60 minutes more frequently in patients with 60-minute TMPG 3 than in patients with TMPG 0 to 2 (54.4% vs 27.8%, $P = .003$). A trend for the association between complete ST resolution and TMPG 3 was present as early as 30 minutes after thrombolytic administration (29.2% vs 15.1%, $P = .069$). The median AUC was reduced in patients with 60-minute TMPG 3 myocardial perfusion, compared with patients with TMPG 0 to 2 (2151.5 μ V-minutes vs 3817.5 μ V-minutes, $P = .01$).

When the analysis was restricted to patients whose CTFC was >40 (signifying slow epicardial culprit artery flow), there was a similar trend for impaired myocardial perfusion with more delayed ST resolution (TMPG 3: median, 64 minutes; IQ, 0/148, n = 14; vs TMPG 0-2: median, 123 minutes; IQ, 95/156; n = 27; $P = .055$). In a separate analysis restricted to patients with an open (TFG 2-3) epicardial artery, the association between delayed ST resolution and impaired TMPGs did not reach statistical significance (for TMPG 3: median, 52 minutes; IQ, 5/95; n = 67 vs for TMPG 0-2; median, 66 minutes; IQ, 4/134 minutes; n = 32; $P = .19$).

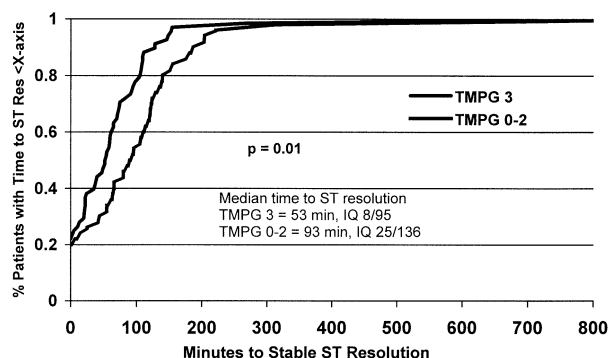
Delayed ST resolution was also associated with abnormal epicardial coronary blood flow (TIMI flow grades 0-2): the median time to complete ST resolution was 108 minutes (n = 47) compared with 46 minutes (n = 72) for TFG 3 ($P = .001$; Figures 3 and 4). A similar pattern was observed when the epicardial flow was analyzed quantitatively with the corrected TIMI frame count. For CTFC >40, the ST resolution occurred at 112 minutes (n = 42) versus 52 minutes (n = 77) for CTFC ≤40 ($P = .0003$; Figures 5 and 6). The presence of both TFG 3 and TMPG 3 (median, 52 minutes; IQ, 11/83 minutes; n = 50) was associated with a reduction in time to ST resolution compared with the absence of both TFG 3 and TMPG 3 (median, 123 minutes; IQ, 95/156 minutes; n = 29) or presence of either TFG 3 or TMPG 3, but not both (median, 55

Figure 1



Shown here for each TMPG are the median times in minutes between the study drug administration and achievement of stable, complete (≥70%) ST-segment resolution on continuous ECG monitoring.

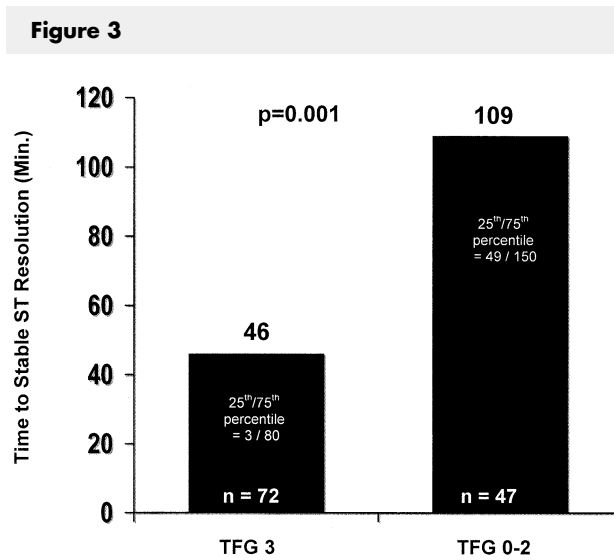
Figure 2



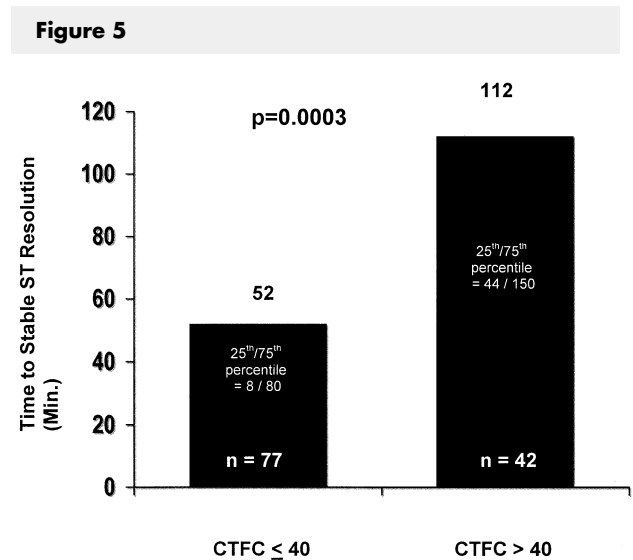
Shown here are cumulative distribution function curves for individual times to stable complete ST-segment resolution. TMPG 3 at 60 minutes is compared with TMPG 0/1/2.

minutes; IQ, 0/91 minutes; n = 39, $P = .0001$ by Kruskal Wallis; $P = .01$ for trend).

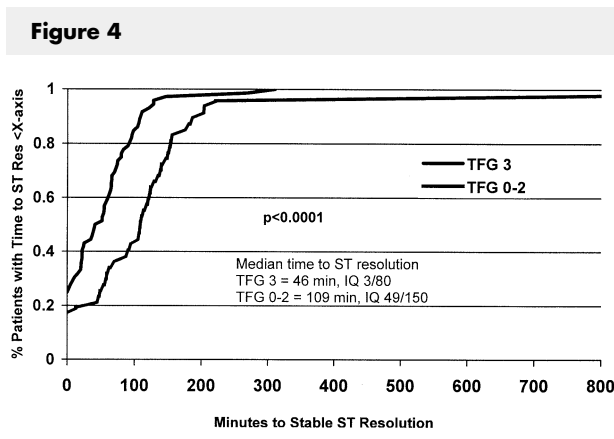
To assess the association of both the percent ST resolution on basis of static ECG and the time-to-resolution on the basis of continuous ST-segment monitoring with angiographic end points in an exploratory analysis, both ST variables were entered into a multivariate model for TFG and a separate multivariate model for TMPG. Both ST variables were entered as continuous variables to achieve better statistical parity in the rela-



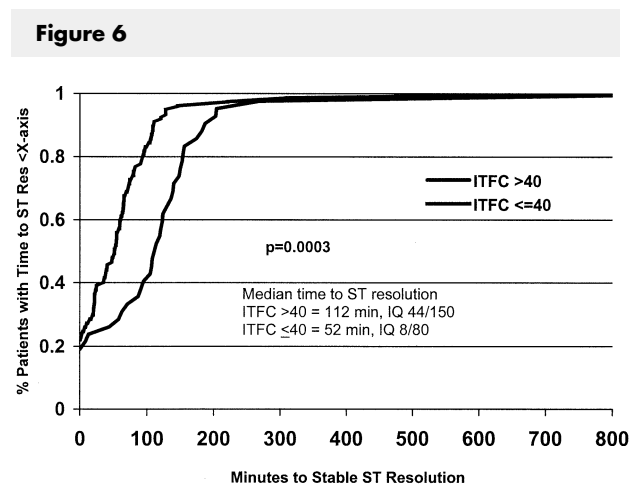
Shown here are the median times in minutes between the study drug administration and achievement of stable, complete ($\geq 70\%$) ST-segment resolution on continuous ECG monitoring. The patients with epicardial TIMI grade 3 flow are compared with patients with TIMI flow grades 0 to 2.



Shown here are the median times in minutes between the study drug administration and achievement of stable, complete ($\geq 70\%$) ST-segment resolution on continuous ECG monitoring. The patients with epicardial CTFCs >40 are compared with patients with CTFCs ≤ 40 .



Shown here are cumulative distribution function curves for individual times to stable complete ST-segment resolution. The patients with epicardial TIMI grade 3 flow are compared with patients with TIMI flow grades 0 to 2.



Shown here are cumulative distribution function curves for individual times to stable complete ST-segment resolution. The patients with epicardial CTFCs >40 are compared with patients with CTFCs ≤ 40 .

tive power of the 2 variables. In the model for TFG 3, both the time-to-ST resolution on continuous ECG (odds ratio [OR], 0.994; $P = .080$) and magnitude of ST resolution at 60 minutes on static ECG (OR, 1.016; $P = .110$) tended to be association with TFG 3, although neither reached statistical significance. In a separate model for TMPG 3, neither time-to-ST resolution on continuous ECG (OR, 0.998; $P = .338$) or magnitude of ST resolu-

tion at 60 minutes on static ECG (OR, 1.015; $P = .102$) reached significance in the association with TMPG 3.

Discussion

Although previous studies have associated persistent ST elevation on the static ECG with impaired epicar-

dial and myocardial perfusion, these results extend these observations to demonstrate that delayed ST resolution on continuous ST-segment monitoring is associated with impaired TIMI myocardial perfusion grades.

Krucoff et al have demonstrated that a reduced likelihood of complete ST resolution on a static 12-lead ECG is associated with reduced TIMI epicardial flow grades.¹⁷ Likewise, a reduced likelihood of complete ST-segment resolution on static ECG has been associated with impaired TIMI myocardial perfusion grades.^{10,11} Krucoff et al have extended these observations to the method of continuous ECG monitoring.¹⁷ They have demonstrated that improved epicardial TIMI flow grades are associated with both a greater likelihood and more rapid speed of ST-segment recovery on continuous ST-segment monitoring.^{8,9} Our data (Figures 3 and 4) confirm these previous findings. No previous studies, however, have evaluated the relationship between the speed of ST-segment recovery and TIMI myocardial perfusion grades. It is notable that both continuous ST-segment recovery patterns and the TIMI myocardial perfusion grades have been associated with subsequent infarct size and left ventricular function and with clinical outcomes.^{2,3,6,7,15}

Because of the dynamic nature of ST-segment resolution, the optimal time to evaluate this measure with a static 12-lead ECG is not well defined.¹ Continuous ST-segment monitoring has been demonstrated to have a stronger association with angiographic patency compared to serial static ECGs.¹⁸ Furthermore, ST elevation may persist even after epicardial artery patency has been restored on the angiogram possibly reflecting persistent impairment of tissue-level perfusion and conferring a poor prognosis.^{4,19} Thus, ST resolution may be an integrative measure of both epicardial and myocardial perfusion. As compared with the static ECG, continuous ST-segment resolution also provides insight into the stability of epicardial and myocardial reperfusion.

In the presence of an open epicardial artery, persistent ST elevation and impaired TIMI myocardial perfusion grades are each associated with a poor prognosis.¹⁵ Indeed, the static ECG and TMPG offer independent prognostic insight into subsequent infarct size, suggesting complementary pathophysiologic mechanisms.²

Limitations

There are several limitations to this study. This is a retrospective analysis of a limited number of patients, and unidentified confounders may have contributed to the findings. This is a report examining correlations in 2 mechanistic biomarkers. Although both the ST-segment recovery and angiographic measures reported here have been shown to be predictive of clinical outcomes in previous studies, adverse outcomes in this

small population were too infrequent (3 patients with death or MI) to be meaningfully analyzed. Finally, strict enrollment criteria are used in clinical trials, and the results observed here may not be applicable to all patients in clinical practice.

Conclusions

While ST resolution on both the static and continuous ECG has been associated with epicardial blood flow, only the static ECG had previously been correlated with myocardial blood flow. This study extends these observations to demonstrate that more rapid ST resolution on continuous ECG monitoring is associated with improved myocardial perfusion after thrombolytic administration. The clinical importance of this mechanistic correlation between biomarkers will require further study from larger data sets.

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