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ST Segment Resolution as a Tool for Assessing the Efficacy of Reperfusion Therapy

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Rapid, simple and inexpensive measures are needed to assess the efficacy of reperfusion therapy both in clinical practice and in clinical trials testing novel reperfusion regimens. In the last decade, several observations have led to a favorable reappraisal of the utility of ST segment monitoring as a simple means of assessing reperfusion in patients receiving fibrinolytic therapy for acute ST elevation myocardial infarction, and ST resolution is being used increasingly in clinical practice and in clinical research. This review focuses on four interrelated roles for ST segment monitoring: the assessment of epicardial reperfusion and the identification of candidates for rescue percutaneous coronary intervention; the evaluation of microvascular and tissue-level reperfusion; the determination of prognosis early after fibrinolytic therapy; and the use of ST segment resolution to compare different reperfusion regimens. (J Am Coll Cardiol 2001;38:1283–94) © 2001 by the American College of Cardiology

In 1969 one of the present authors and his collaborators demonstrated that myocardial ischemic injury after coronary artery occlusion is not fixed but can be influenced profoundly by altering the balance between myocardial oxygen supply and demand (1). In dogs with occluded coronary arteries, the magnitude of ST segment elevation correlated well with subsequent depression of myocardial creatine kinase activity (2) and with evidence of myocardial necrosis on histologic examination (2,3). The height of the ST segment on epicardial electrocardiograms (ECG) was, therefore, utilized as an index of the severity of ischemic injury. In considering how this approach could be utilized clinically, extension from the epicardial to the surface ECG was considered, and a close correspondence between the precordial and epicardial ECG was described (3,4) (Fig. 1).

In the dog with coronary occlusion, myocardial reperfusion was accompanied by rapid normalization of ST segment elevation (5). A decade later, with the clinical development of thrombolytic therapy for acute myocardial infarction (MI), similar observations were made in humans (6). ST segment resolution was subsequently evaluated in a number of studies to determine its accuracy for predicting patency of the infarct-related artery (IRA) (7–11), but no clear consensus was reached on the utility of this measurement. Thus, coronary angiography has remained the "gold standard" for identifying promising reperfusion regimens that merit evaluation in large phase III trials.

In the last decade, several observations have led to a reappraisal of the utility of ST segment monitoring after ST elevation MI (STEMI). First, Schröder and colleagues (12,13) showed that ST segment resolution can predict accurately the risk for death and congestive heart failure (CHF) in patients treated with fibrinolytic therapy (12,13). Subsequent studies confirmed a remarkably consistent relationship between the degree of ST resolution and subsequent mortality (Fig. 2). Second, Ito et al. (14,15) demonstrated that restoration of normal epicardial blood flow is not sufficient to ensure adequate myocardial reperfusion; the latter requires perfusion at the level of the coronary microcirculation and myocytes. Novel reperfusion regimens have been developed that incorporate both fibrinolytic and antiplatelet therapies (16–18), and these therapies may be particularly effective in the coronary microcirculation (19,20).

Resolution of ST segment elevation is now being used with increasing frequency in clinical trials and patient management. This review will focus on four interrelated roles for ST segment monitoring:

1. Assessment of epicardial reperfusion and identification of candidates for rescue percutaneous coronary intervention (PCI);
2. Evaluation of microvascular and tissue-level reperfusion;
3. Determination of prognosis early after fibrinolytic therapy; and
4. Direct comparison of different reperfusion regimens.

IDENTIFICATION OF CANDIDATES FOR RESCUE PCI

Patients who fail to achieve normal Thrombolysis In Myocardial Infarction (TIMI) grade 3 epicardial blood flow after fibrinolytic therapy are at high risk for the development of death and CHF (21,22). Data to support urgent "rescue" PCI in patients with an occluded infarct artery are limited to retrospective studies (23,24) and several small randomized clinical trials (25). Unfortunately, it has become extremely difficult to study directly the efficacy of rescue PCI because, after identifying an occluded IRA by angiography, most investigators are not willing to randomize patients to a

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Abbreviations and Acronyms

CHF	= congestive heart failure
GP IIb/IIIa	= glycoprotein IIb/IIIa
GUSTO	= Global Use of Strategies to Open Occluded Coronary Arteries trial
IRA	= infarct-related artery
MI	= myocardial infarction
MRI	= magnetic resonance imaging
PCI	= percutaneous coronary intervention
PET	= positron emission tomography
STEMI	= ST elevation myocardial infarction
TIMI	= Thrombolysis In Myocardial Infarction
tPA	= tissue plasminogen activator

strategy that does not involve PCI (26). Although the studies to date have major limitations, the weight of evidence supports the value of rescue PCI in moderate- to high-risk patients with an occluded IRA after fibrinolytic therapy (26). Furthermore, it is likely that the relative benefits of rescue PCI have increased in the modern interventional era due to the introduction of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors (27), stenting (28) and improved vascular access site management. These advances should decrease the probability of failed rescue PCI, which is associated with mortality rates as high as 30% to 50% (23,24,29–31).

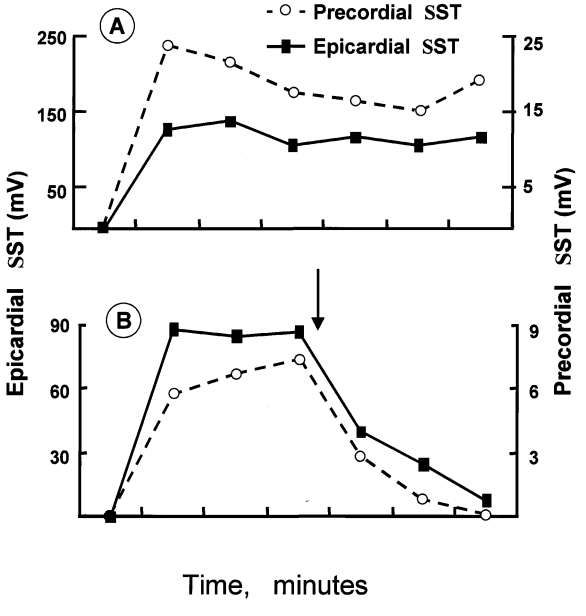

Figure 1. Examples of the correspondence between the sum of ST segment elevations (ΣST) from epicardial leads and the ΣST from precordial leads at 5-min intervals after experimental coronary artery occlusion. **(A)** Correlation between epicardial ΣST and precordial ΣST when the occlusion was maintained. **(B)** correlation between epicardial ΣST and precordial ΣST when one of the two occlusions was released at 15 min **(arrow)**. Note the marked fall in both epicardial and precordial ΣST after reperfusion of the larger of the two vessels. Adapted from Muller JE, Maroko PR, Braunwald E. Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischemic injury. Circulation 1975;52:16–27.

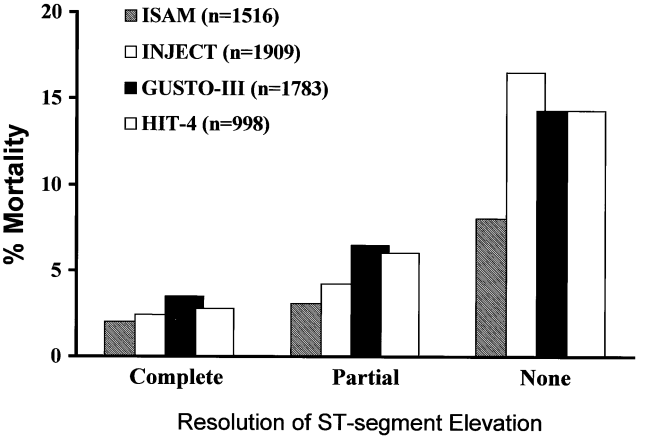

Figure 2. ST segment resolution 180 min after administration of therapy and mortality (at time points between 21 to 35 days) in four trials of thrombolytic therapy in acute myocardial infarction. All studies found statistically significant mortality differences between the three groups of ST resolution. GUSTO-III = Global Use of Strategies to Open Occluded Coronary Arteries study; HIT-4 = Hirudin for Improvement of Thrombolysis (HIT)-4 study; INJECT = International Joint Efficacy Comparison of Thrombolytics study; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction. Data abstracted from references 12, 13 and 40. The GUSTO-III data are abstracted from Anderson R, White H, Ohmann E, et al. Resolution of ST segment elevation 90 minutes after thrombolysis for acute myocardial infarction predicts outcome: a GUSTO III substudy (abstr). J Am Coll Cardiol 1998;31 Suppl A:371A.

The role of rescue PCI for patients with TIMI grade 2 flow is less well established, because residual stenosis and thrombosis may play only a contributory role in the pathogenesis of TIMI grade 2 flow. Many patients with TIMI grade 2 flow after reperfusion therapy have sluggish flow on the basis of increased microvascular resistance rather than a flow-limiting epicardial stenosis (32). Two small randomized trials of rescue PCI have been performed among patients with TIMI grade 2 flow (26,33), and neither has demonstrated an improvement in clinical outcomes. Thus, larger, prospective trials are needed to address this important question.

To identify appropriate candidates for rescue PCI, rapid, simple and readily available bedside measures of the success or failure of epicardial reperfusion are needed. ST resolution has been extensively evaluated for this purpose (7–11). Early studies were limited by small size, the use of different measurement techniques and definitions for ST resolution, varying time points for ECG and angiographic measurements and the retrospective definition of thresholds for ST resolution. Despite these important methodologic differences, the aforementioned studies yielded remarkably similar results, suggesting that ST resolution is a highly accurate predictor of infarct artery patency (positive predictive value ≥90%) but inaccurate for predicting IRA occlusion (negative predictive value approximately 50%) (10,11,34–36).

In the largest studies comparing angiographic measures of reperfusion with simultaneous measurements of ST resolution, a significant stepwise correlation has been observed between greater ST resolution and higher rates of IRA patency and TIMI grade 3 flow (37,38) (Fig. 3). After

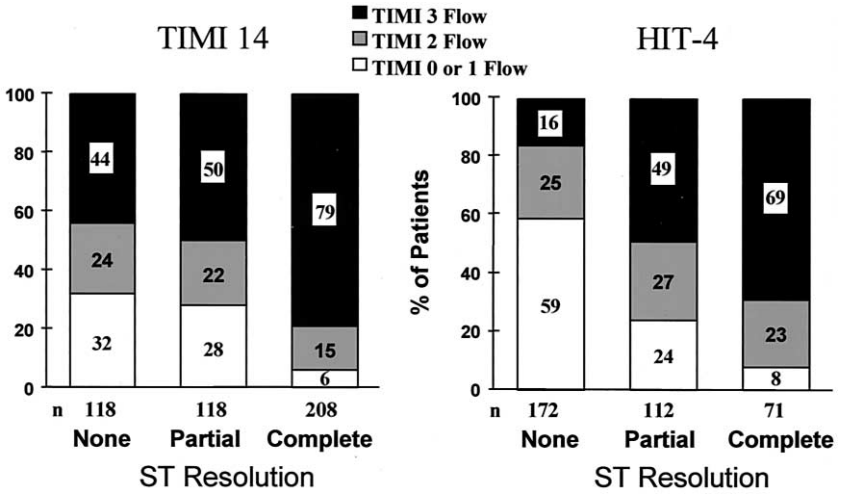

Figure 3. ST resolution versus Thrombolysis In Myocardial Infarction (TIMI) flow grade. The reperfusion regimens used in the TIMI-14 substudy were tissue plasminogen activator (tPA) and combinations of abciximab plus reduced-dose tPA, whereas the fibrinolytic agent used in Hirudin for Improvement of Thrombolysis study (HIT-4) was streptokinase. $p < 0.001$ for the correlation between ST resolution and TIMI 3 flow; $p < 0.001$ for correlation between ST resolution and infarct-related artery patency (TIMI 2 + 3 flow). Adapted from references 37 and 38.

tissue plasminogen activator (tPA), 35% to 40% of patients achieve complete (≥70%) ST resolution 90 min after therapy, as defined using Schröder's criteria (20,39); in contrast, after streptokinase, only approximately 25% of patients achieve complete ST resolution at 90 min (40). By 180 min, differences between the two agents are no longer apparent, as tPA and streptokinase each achieve complete ST resolution in approximately 50% of patients (39,40).

Despite differences between tPA and streptokinase in the proportion of patients who achieve complete ST resolution 90 min after therapy, the correlation between ST resolution and epicardial blood flow at 90 min is similar for the two drugs (Fig. 3). Patients with complete ST resolution at 90 min have a 92% to 94% likelihood of IRA patency and a 70% to 80% probability of TIMI grade 3 flow (37,38). However, the absence of ST resolution does not accurately predict an occluded IRA in that approximately 50% of patients with no (<30%) ST resolution still have a patent IRA (37,38). Previously, the absence of ST resolution despite a patent IRA had been considered to be a false positive of the 12-lead ECG. As will be discussed in the following text, in such patients, the ECG, rather than the angiogram, may better reflect the adequacy of myocardial reperfusion.

Impact of infarct location on the relationship between ST resolution and TIMI flow grade. Important differences exist between anterior and inferior MI with regard to ST segment resolution (8,9,12,13,38,41,42). Patients with anterior infarction develop significantly less ST resolution than those with inferior infarction, despite only modest differences in epicardial blood flow, suggesting that ST resolution is a less accurate predictor of epicardial reperfusion among patients with anterior versus inferior MI (8,12,13,38,41). This may be due to technical factors, such as the frequent (normal) presence of J point elevation in the anterior precordial leads (43), which would serve to decrease the extent of ST segment resolution that is possible. Additionally, anterior MI typically is associated with a larger infarct size and greater tissue injury than inferior MI. As a result, different threshold levels of ST resolution may be appropriate for anterior versus inferior MI (38,41). When sensitivity analyses are performed, it appears that resolution of ST deviation by ≥70% is the optimal threshold for patients with inferior MI, whereas resolution by ≥50% may be optimal for anterior MI (38). As will be discussed in the following text, however, these threshold effects are probably relevant only with regard to the prediction of IRA patency. In terms of prognosis, a greater degree of ST resolution is associated with lower mortality for both anterior and inferior infarction (12,13).

Differentiating TIMI flow grade 2 from TIMI flow grade 3. Patients with TIMI grade 3 flow demonstrate significantly greater ST resolution than patients with TIMI grade 2 flow (36–38,44) (Fig. 4). Yet, among patients with complete (≥70%) ST resolution, the probability of TIMI grade 3 flow is only 70% to 80% (vs. an approximately 95% probability of TIMI grade 2 + 3 flow). Thus, while "complete" ST resolution confirms that the infarct artery is patent, it does not confirm that TIMI grade 3 flow is present with >80% accuracy (36,37) (Fig. 3). However, mortality appears to be similar between patients with TIMI grade 2 flow and TIMI grade 3 flow if they have similar degrees of ST resolution (38).

Combination of ST resolution with other noninvasive predictors of failed reperfusion. Given the limitations of using ST resolution alone to identify patients with failed epicardial reperfusion, efforts have been made to evaluate other noninvasive predictors of IRA patency, including chest pain resolution and rapid washout of serum cardiac biomarkers (10,35,36,45,46). Although persistent chest pain after fibrinolytic therapy does identify patients who are significantly more likely to have an occluded infarct artery or

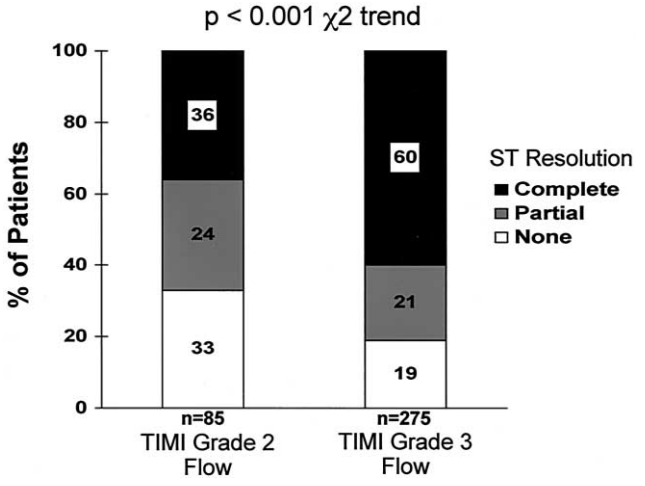

Figure 4. Differences in ST resolution between patients with Thrombolysis In Myocardial Infarction (TIMI) grade 2 and TIMI grade 3 epicardial blood flow. Adapted from de Lemos JA, Antman EM, McCabe CH, et al. ST segment resolution and infarct related artery patency and flow after thrombolytic therapy. Am J Cardiol 2000;85:299–304.

<TIMI grade 3 flow (9,45,47–49), this subjective measure is not sufficiently accurate to guide clinical decision making independent of other criteria (10,45,49). Of the cardiac biomarkers studied to date, early release of myoglobin appears to be superior to creatine kinase MB and the cardiac-specific troponins for the assessment of reperfusion, due to its cytosolic location, small size and rapid release and washout (50–54). Assessment of the rate of increase in serum myoglobin over the first 60 to 90 min after fibrinolysis, or the ratio of myoglobin at 60 or 90 min/baseline, appears to allow early assessment of IRA patency (50–54). The use of more specific, even smaller molecules for this purpose, such as heart-type fatty acid binding protein, does not appear to improve predictive accuracy versus myoglobin (55). Prediction of the status of the IRA using cardiac biomarkers suffers from the same limitations as ST segment analysis, namely that the there are many "false positive" diagnoses of failed fibrinolysis (46,49,50).

Several studies have integrated cardiac biomarker data with ST resolution and other clinical data to improve the predictive accuracy for noninvasive identification of candidates for rescue PCI (35,56). We have recently shown that ST resolution, chest pain resolution and the concentration of serum myoglobin can be used together to predict failure of epicardial reperfusion (49). We prospectively identified three criteria for failed epicardial reperfusion: ST resolution <50% at 90 min, persistent chest pain at 90 min and a 60 min/baseline ratio of serum myoglobin <4. The 12% of patients who satisfied all three criteria had a 76% probability of failing to achieve TIMI grade 3 flow in the infarct artery 90 min after fibrinolysis and a 57% probability of having an occluded infarct artery (Fig. 5); on the other hand, the approximately 60% of patients who satisfied 0 or 1 of these criteria had only a 6% or lower probability of IRA occlusion, an approximately 20% probability of achieving < TIMI grade 3 flow and a 30-day mortality of approximately 1%

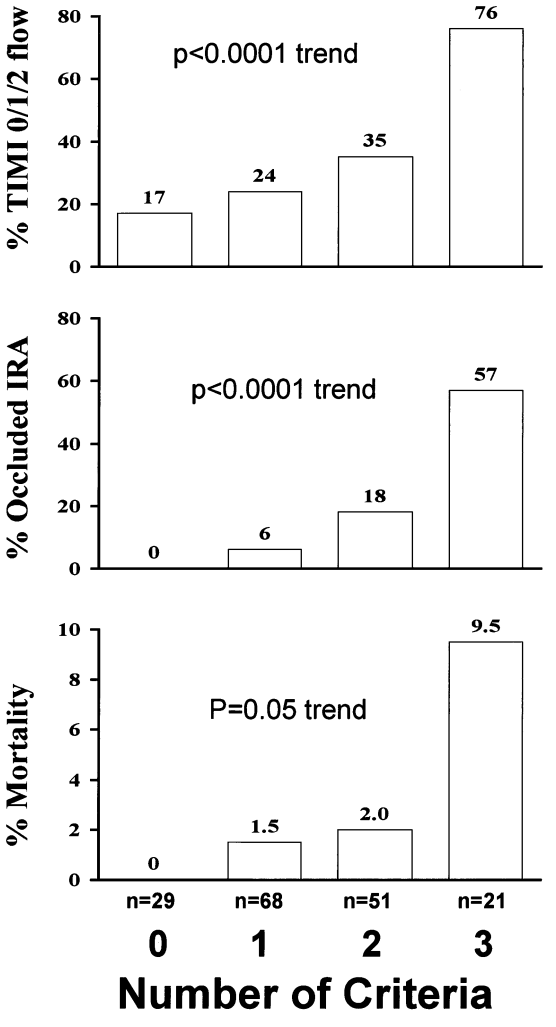

Figure 5. Correlation between noninvasive predictors of failed epicardial reperfusion and infarct artery patency, flow and mortality. The three noninvasive criteria for failed reperfusion are: ST resolution <50% at 90 min, 60 min/baseline ratio of serum myoglobin <4 and persistent chest pain at the time of coronary angiography. IRA = infarct-related artery; TIMI = Thrombolysis In Myocardial Infarction. Reproduced with permission from de Lemos JA, Morrow DA, Gibson CM, et al. Early noninvasive detection of failed epicardial reperfusion after fibrinolytic therapy. Am J Cardiol 2001;88:353–8.

(Fig. 5). Even when used in combination, these noninvasive criteria remain limited by false positive diagnoses of failed epicardial reperfusion; however, using these criteria in combination clearly improves prediction versus the use of these criteria individually. A potential algorithm for detecting failed epicardial reperfusion is shown in Figure 6.

ST RESOLUTION AS A MARKER OF MYOCARDIAL AND MICROVASCULAR REPERFUSION

The previous discussion addressed the practical question of how best to identify patients with failure of epicardial reperfusion. Even among those who achieve normal epicardial flow, however, tissue-level perfusion may be inadequate. Using myocardial contrast echocardiography, it has been demonstrated that many patients with successful epicardial

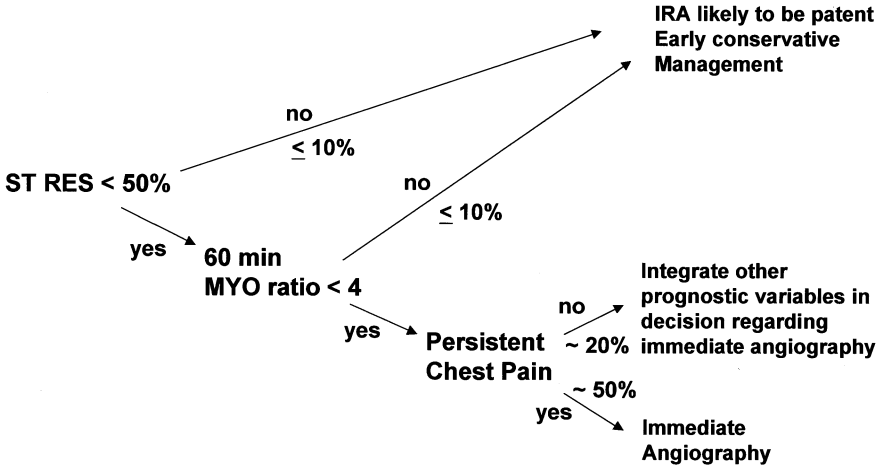

Figure 6. Proposed algorithm for the noninvasive detection of failed epicardial reperfusion. Percentages shown are the expected proportion of patients with an occluded infarct artery (Thrombolysis In Myocardial Infarction [TIMI] 0/1 flow). IRA = infarct-related artery; MYO = myoglobin; ST RES = ST resolution.

reperfusion have "no reflow" at the level of the coronary microcirculation and myocardium (14). Patients with TIMI grade 3 flow in the infarct artery, but no-reflow at the tissue-level, have poor recovery of left ventricular function after MI and are at high risk for the development of CHF and death (14). Investigators have confirmed these observations using other measures of tissue perfusion, including Doppler flow-wire measurements (19), nuclear scintigraphy (57), cardiac magnetic resonance imaging (MRI) (58) and positron emission tomography (PET) scanning (59). Recently, novel angiographic measures of microvascular "blush" have been developed that provide risk stratification independent of TIMI flow grade (60,61).

Taken together, these studies challenge the concept that TIMI grade 3 flow alone is indicative of successful reperfusion and suggest that markers of myocardial and microvascular perfusion will provide additive and independent prognostic value. Since none of the aforementioned imaging tests is readily available to the clinician at the bedside, ST resolution has re-emerged as a simple and universally available means of assessing tissue-level reperfusion. Studies using both contrast echocardiography and angiographic "blush" scores have shown that, among patients with normal epicardial blood flow, persistent ST elevation is usually indicative of impaired tissue and microvascular perfusion (60,62,63).

ST SEGMENT RESOLUTION AND PROGNOSIS

Early studies using ST segment resolution demonstrated that patients with rapid ST resolution had smaller infarcts than those with persistent ST elevation (8). Substudies from several large trials have further evaluated the relationship between ST resolution and clinical end points. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) investigators, in a study of 7,426 patients, found that two-thirds of patients had ≥50% ST resolution 4 h after thrombolysis; these patients had a 30-day mortality rate of 3.5% versus 7.4% in the patients with <50% ST resolution (64). Schröder et al. (12,13,40) have used a three-component definition for resolution of the sum of ST elevation 180 min after fibrinolysis: complete (≥70%), partial (30% to <70%) and none (<30%). In a series of large fibrinolytic trials, these investigators have demonstrated a strong, stepwise correlation between the degree of ST resolution at 180 min and subsequent mortality (12,13,40) (Fig. 2).

More recently, it has been shown that an assessment of ST resolution even earlier than 3 to 4 h after the onset of fibrinolytic therapy can be used for risk stratification; both 60- and 90-min determinations of ST resolution provide excellent discrimination of the risk for death and CHF in patients receiving tPA-based fibrinolytic regimens (65–68) (Table 1). Furthermore, it appears that patients who develop complete ST resolution by 60 min are at even lower risk for death and heart failure than those who develop complete ST resolution by 90 min (68). Because of the slower onset of fibrinolytic activity with streptokinase, 90 min appears to be too early to make a definitive statement on ST resolution with this agent; 180 min may be a more appropriate time to assess the efficacy of reperfusion with streptokinase (40).

In addition to its ability to predict mortality, the degree of ST resolution also predicts the development of left ventricular dysfunction and clinical CHF. More complete ST resolution consistently has been associated with smaller infarct size and improved left ventricular function (8,42,69,70). Similar to mortality, the probability of CHF decreases in a stepwise fashion with greater degrees of ST segment resolution (12,13,42,67,68,71,72) (Table 1).

Of particular importance is the observation that the prognostic power of ST resolution persists even after accounting for the effects of epicardial blood flow. In the

Table 1. Comparison of 60- and 90-min Measurements of ST Resolution

Outcome	ST Resolution			p Trend
	Complete (≥70%)	Partial (30% to <70%)	None (<30%)	
60 min ST resolution:				
n	295 (33%)	268 (30%)	337 (37%)	
Death, 30 days (%)	1.7	4.5	7.7	0.002
Death, 1 year (%)	2.7	7.5	10.7	0.0005
CHF, 30 days (%)	7.1	13.8	17.2	0.0007
90 min ST resolution:				
n	318 (41%)	243 (32%)	203 (27%)	
Death, 30 days (%)	3.1	5.3	8.9	0.02
Death, 1 year (%)	4.7	7.4	11.3	0.02
CHF, 30 days (%)	8.5	12.8	15.3	0.05

Adapted from de Lemos JA, Antman EM, Giugliano RP, et al. Comparison of a 60 versus 90-min determination of ST-segment resolution after thrombolytic therapy for acute myocardial infarction. Am J Cardiol 2000;86:1235–7.
CHF = congestive heart failure.

TIMI 14 substudy described in the preceding text, among patients with a patent infarct artery 90 min after thrombolysis, those with <70% ST resolution had a tenfold increase in mortality versus those with complete (≥70%) ST resolution (38). Interestingly, when patients were characterized as to whether they had complete (≥70%) or incomplete (<70%) ST resolution, there was no difference in mortality between patients with TIMI grade 2 flow and TIMI grade 3 flow (38). Using continuous ST monitoring, the Hirulog Early Reperfusion/Occlusion-1 investigators have shown that patients with early, stable ST recovery have improved infarct zone wall motion, independent of TIMI flow grade (72). In a substudy from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI)-7 and the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-1 trials, ST resolution, but not TIMI flow grade, was an independent predictor of mortality and CHF (71).

Additional support for the independent prognostic value of ST resolution comes from the experience with primary PCI for STEMI. After successful primary PCI, in which TIMI grade 3 flow is established in the infarct artery, persistent ST elevation is associated with poor recovery of left ventricular function and increased mortality (70,73–75). Patients with an increase in ST elevation after PCI (ST segment re-elevation) appear to be at even higher risk for the development of death and heart failure due to extensive infarction, distal embolization or reperfusion injury (74,76–78).

Taken together, these studies support the hypothesis that ST resolution is a surrogate for tissue-level reperfusion. When "complete" ST resolution is seen 90 min after fibrinolysis, successful reperfusion has occurred at both the epicardial and microvascular level, and the prognosis is excellent. Persistent ST elevation, on the other hand, appears to be indicative of either an occluded IRA or a patent artery with failure of myocardial and microvascular reperfusion.

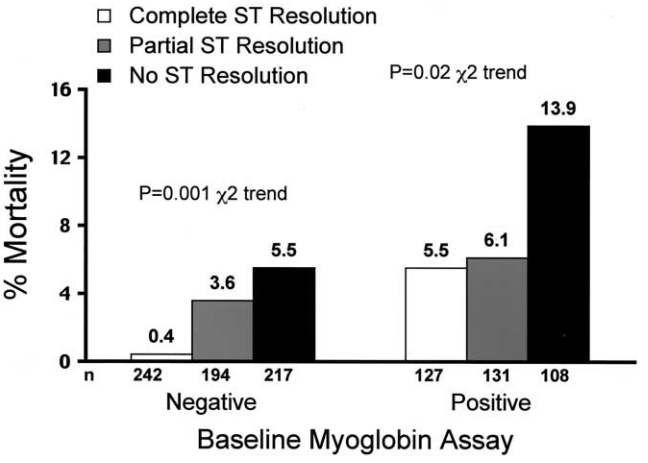

Figure 7. Stratified analyses of 30-day mortality based on the status of a bedside myoglobin assay performed immediately before fibrinolysis, and ST resolution, measured 60 to 90 min after fibrinolysis. ST RES = ST resolution. Adapted with permission from de Lemos JA, Antman EM, Giugliano RP, et al. Very early risk stratification after thrombolytic therapy with a bedside myoglobin assay and the 12-lead electrocardiogram. Am Heart J 2000;140:373–8.

Integration with other prognostic markers in ST elevation MI. Baseline clinical variables such as age, body weight, infarct location, time to treatment, evidence for CHF or shock, and the presence of diabetes, hypertension or prior coronary artery disease can be used to predict the risk for death among patients presenting with STEMI (79). In studies performed to date, greater ST resolution is predictive of lower mortality in both high- and low-risk subsets defined using clinical factors, and is also an independent risk predictor in multivariate models (12,13,40,67). Recently, it has been shown that additional prognostic information can be obtained from the level of cardiac biomarker elevation before the administration of fibrinolytic therapy. Patients with an elevated myoglobin (67) or cardiac troponin T (80–82) concentration before fibrinolysis are at high risk for development of death and CHF due to extensive myocardial necrosis that had developed before therapy was initiated. A handheld myoglobin assay performed at the bedside immediately before fibrinolysis and ST resolution assessed 60 to 90 min after the onset of therapy can be used in combination to predict risk in patients with STEMI; these two markers provide prognostic information that is independent of baseline clinical markers of risk, and discriminate a 25-fold gradient of risk within 90 min of fibrinolysis (67) (Fig. 7).

THE USE OF ST RESOLUTION TO COMPARE DIFFERENT REPERFUSION REGIMENS

Due to its ease of use and universal availability, ST resolution has long been considered as a potentially useful means of comparing different therapies for ST elevation MI. In a retrospective analysis of data from the Intravenous Streptokinase in Acute Myocardial Infarction trial, Schröder et al. (12) found greater ST segment resolution among patients

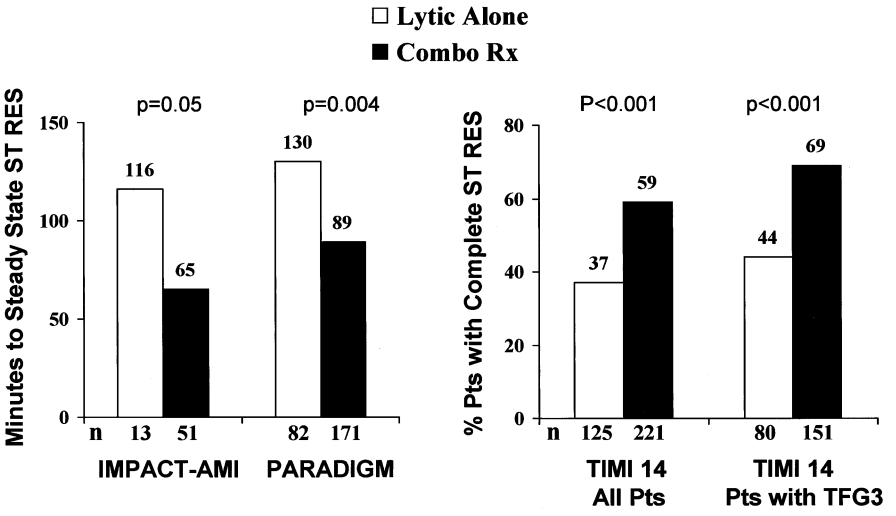

Figure 8. Overview of studies using ST resolution (ST RES) to compare standard fibrinolytic therapy with reperfusion regimens containing glycoprotein IIb/IIIa inhibitors and reduced doses of fibrinolytics (combination therapy). In the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-Acute Myocardial Infarction (IMPACT-AMI) and Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) studies, where continuous ST monitoring was performed, combination therapy was associated with more rapid ST recovery than was standard fibrinolytic therapy. In the Thrombolysis In Myocardial Infarction (TIMI) 14 study, where static ST monitoring was performed, combination therapy was associated with a greater likelihood of achieving complete (≥70%) ST resolution, even after limiting the analysis to patients with normal (TIMI grade 3) epicardial blood flow. Pts = patients; TFG3 = TIMI grade 3 flow. Adapted from references 16, 20 and 83.

who received streptokinase than among those who received placebo; in the overall trial, there was a similar trend in mortality favoring streptokinase. Similar observations were made in the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial, in which reteplase was associated with greater ST resolution and a trend towards lower mortality than streptokinase (13). Other small trials, not powered for mortality, have incorporated ST segment analysis into composite assessments of clinical efficacy (16,83,84).

Several factors have increased interest in using ST resolution as a surrogate efficacy measure in reperfusion trials. First, measurement of epicardial flow using coronary angiography, the "gold standard" used to identify promising reperfusion regimens for testing in large mortality trials, has proven disappointing in its ability to distinguish different reperfusion regimens and doses. For example, a phase II trial (85) found a higher rate of TIMI grade 3 flow with reteplase than with alteplase, but this agent was not associated with a lower mortality than alteplase in a large phase III study (86). Second, as discussed above, ST resolution has been shown to provide prognostic information independent of epicardial blood flow because it also reflects tissue and microvascular perfusion. As such, it may be a better surrogate marker than epicardial blood flow (71) and, at the very least, appears to provide complementary information for assessing therapeutic efficacy. Finally, certain therapies may be particularly beneficial in the coronary microcirculation. For example, Neumann et al. (19) demonstrated that, among patients undergoing PCI for MI, Doppler peak flow velocity (a measure of microvascular function) was improved over 14 days in patients who received adjunctive therapy with the platelet GP IIb/IIIa inhibitor abciximab. This finding was accompanied by improved regional and global left ventricular function.

ST resolution has been used to evaluate newer reperfusion regimens that incorporate combinations of GP IIb/III inhibitors and fibrinolytics (Fig. 8). In the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-Acute Myocardial Infarction study (IMPACT-AMI), combination therapy with eptifibatide and alteplase improved the time to steady state ST recovery versus alteplase alone (16) (Fig. 8). Similarly, in the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction trial (PARADIGM), lamifiban improved ST resolution when given in combination with fibrinolytic therapy (83) (Fig. 8). The TIMI 14 trial compared the combination of abciximab and reduced doses of fibrinolytics with full-dose fibrinolytics alone. In the primary outcome analysis of the study, the combination of abciximab and reduced-dose alteplase (tPA) resulted in a significant improvement in epicardial flow (increased TIMI grade 3 flow rates and lower TIMI frame counts at 60 and 90 min) when compared with tPA alone (17). All 346 patients with interpretable baseline and 90 min ECGs treated with either tPA alone or abciximab plus reduced-dose tPA (combination therapy) were included in an ST resolution substudy (20). Patients who received combination therapy had a higher probability of complete ST resolution than those receiving tPA alone (59% vs. 37%; $p < 0.0001$) (Fig. 8). Even after controlling for differences in epicardial blood flow, patients receiving combination therapy had significantly greater ST resolution than those receiving tPA alone (Fig. 8). This benefit appeared to be present regardless of the fibrinolytic agent and dose used, suggesting that this effect was due to abciximab rather than

the fibrinolytic agent. It was concluded that combination therapy with abciximab and reduced-dose fibrinolytic therapy improved myocardial perfusion in addition to epicardial flow (20). The promising findings with combination reperfusion therapy were confirmed in two companion studies, which evaluated abciximab with reduced-dose reteplase instead of alteplase (18,87). A large phase III trial, GUSTO-V, recently reported 30-day safety and efficacy outcomes for this reperfusion strategy. Patients randomized to receive combination therapy with abciximab and reduced-dose reteplase had a nonsignificant 0.3% reduction in 30-day mortality versus patients randomized to reteplase alone (88). The results of long-term follow-up in this study, as well as the results of other ongoing trials evaluating different combinations of GP IIb/IIIa inhibitors and fibrinolytics, are eagerly awaited.

In a related analysis from the TIMI 14 study, the degree of ST segment resolution after early adjunctive PCI was determined. Among patients who underwent adjunctive PCI between 90 and 180 min after fibrinolysis, those who had initially been treated with a combination regimen containing abciximab had significantly greater ST resolution after PCI and a lower likelihood of ST re-elevation than patients who had been treated with a fibrinolytic alone (89). Furthermore, the percutaneous procedure itself was associated with enhanced ST resolution among patients who had received abciximab but not those who had received a fibrinolytic alone (89) (Fig. 9). These findings suggest that abciximab may prevent the microvascular injury that frequently occurs when adjunctive PCI is performed early after the administration of fibrinolytic therapy.

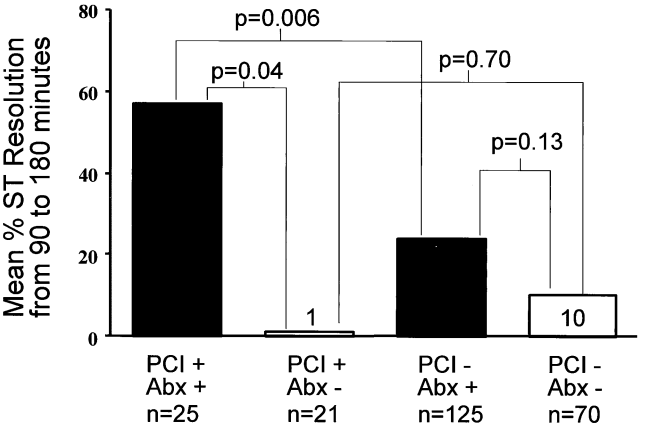

Figure 9. Subset of patients from the Thrombolysis In Myocardial Infarction (TIMI) 14 trial with TIMI grade 3 flow in the infarct artery at 90 min. Comparison of mean percent ST resolution from 90 to 180 min between patients who did and did not undergo early adjunctive percutaneous coronary intervention (PCI) between 90 to 180 min after fibrinolysis. Patients are further separated into those who received and did not receive abciximab (Abx) as part of the reperfusion regimen. In the presence of Abx pretreatment, early adjunctive PCI was associated with greater ST resolution, whereas in the absence of Abx pretreatment, ST resolution tended to be worse in patients who underwent PCI. Reproduced with permission from de Lemos JA, Gibson CM, Antman EM, et al. Abciximab and early adjunctive percutaneous coronary intervention are associated with improved ST segment resolution after thrombolysis: observations from the TIMI 14 trial. Am Heart J 2001;141:592–8.

METHODOLOGIC CONSIDERATIONS

Single lead versus sum of ST segments. Investigators have used a variety of different techniques for measuring ST deviation including choosing the single lead with the greatest baseline ST deviation, summing some or all leads with ST elevation and summing both ST elevation and reciprocal ST depression. Although few direct comparison studies are available, single-lead techniques appear to provide comparable results to multilead techniques for the prediction of epicardial patency, provided the lead is left in an identical position from tracing to tracing (90). However, single-lead techniques may not be sufficient for prognostic assessment. To date, the large prognostic trials (12,13,40,66,73) and the studies comparing ST resolution with specific indexes of microvascular perfusion (60,62,63) have utilized sums of ST deviation from standard 12-lead ECGs. Comparative studies are needed in which single-lead and multiple-lead measurements are prospectively defined and directly compared.

Static versus continuous ST monitoring. This discussion has focused primarily on the use of static ST segment monitoring—the comparison of two ECGs 60 to 180 min apart. However, the use of only two static ECGs has several important limitations. First, the actual peak of ST deviation may be missed, and, as a result, the degree of ST resolution may be underestimated (90), contributing to the high "false positive" rate for coronary occlusion that has been observed. Second, coronary reperfusion is a dynamic process with transient changes in epicardial flow patterns observed frequently in the early hours after reperfusion (48). Reocclusion also occurs frequently after initially successful fibrinolysis, is often asymptomatic and is associated with a significant increase in the risk for adverse events (91,92). Continuous ST segment monitoring can overcome some of the limitations of static ST monitoring and improves the likelihood of capturing the maximal point of ST deviation as well as early episodes of reocclusion that are manifest by recurrent ST elevation (9,90,93–95). ST segment re-elevation that occurs 6 to 24 h after fibrinolysis appears to be independently associated with worse outcomes (96). The variable that appears to be most predictive using continuous ST monitoring is the time to steady state ST recovery, usually defined as $\geq$50% reduction of the ST elevation in the single lead with greatest peak ST elevation, without episodes of early ST re-elevation (34,48,90,95,97). Unfortunately, continuous ST monitoring is not widely available, requires additional personnel and training, and may be difficult to perform rapidly in acutely ill patients. In addition, studies of continuous ST monitoring performed to date have been designed to address the question of IRA patency rather than prognosis.

We recommend that frequent static ST monitoring be performed after fibrinolytic therapy in the majority of

centers where high-quality continuous ST monitoring is not currently available. Twelve-lead ECGs should be performed immediately before fibrinolysis and then at 60 and 90 min after fibrinolysis. After treatment with streptokinase, later measurements (at 90 and 180 min) of ST resolution are probably more appropriate. Electrocardiograms should be obtained serially at least every 6 to 8 h through the first 24 h to assess for silent reocclusion. Alternatively, continuous ST monitoring may be particularly effective in the time period from 3 to 24 h after fibrinolysis, when the goal of ST monitoring shifts towards the detection of silent reocclusion. Here, the technical challenge of rapidly placing a continuous ST monitor is likely to be a less important limitation than it is in the early phase of infarction, when continuous ST monitoring may be too cumbersome for widespread clinical use.

FUTURE DIRECTIONS

The resurgent interest in using ST resolution as a bedside marker of reperfusion has stimulated additional research in this area. The results from the TIMI 14, PARADIGM and IMPACT-AMI trials, taken together with the large outcome trials from Schröder and others, suggest that ST resolution may be a suitable surrogate marker for phase II trials testing novel reperfusion regimens. Replacing angiography with ST resolution may allow these trials to be performed at lower expense and perhaps with more precision. The Fibrinolytics and Aggrastat with ST Elevation Resolution trial is a phase II study comparing tenecteplase with the combination of tirofiban and reduced-dose tenecteplase. The dose-confirmation phase of this study will utilize an ST resolution measurement as the primary end point.

Several important caveats require mention with regard to trial design. As noted above, ST segment resolution differs between anterior and inferior infarction (38), and studies that do not account for these differences may yield invalid results. Of note, Gibson et al. (98) reported that epicardial blood flow is also slower with infarcts in the region of distribution of the left anterior descending artery than infarcts in the other arterial beds (98). Due to these differences, we recommend that, in phase II trials comparing novel thrombolytic regimens, a stratified randomization scheme be used for subjects with anterior versus nonanterior infarction.

Additional work is needed to clarify the relationship between ST segment resolution and other indexes of microcirculatory function, including contrast echocardiography, MRI, nuclear scintigraphy, PET scanning and Doppler flow-wire techniques. Future trials that evaluate these imaging modalities should incorporate measures of ST segment resolution to help clarify the relationship between simple bedside measures and the more complex and expensive imaging modalities. Additionally, ST resolution may be particularly useful in the study of novel adjunctive therapies, such as those designed to provide myocardial protection and prevent reperfusion injury. Finally, on a more practical level, more research is needed in which ST resolution is combined with other noninvasive measures of reperfusion to help clinicians make real-time decisions about which patients should be taken emergently for "rescue" PCI.

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