ST Segment Elevation Resolution after Thrombolytic Therapy in Acute Myocardial Infarction

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Thrombolytic therapy has been shown in randomized controlled trials to improve the natural history of acute myocardial infarction, with an approximate 30% reduction in mortality [1–5]. Angiographic studies such as GUSTO-1 [6], TEAM-2 and 3, and TIMI-4 demonstrated that to reduce mortality with thrombolysis, there are two *sine qua non* conditions to be resolved: a patent epicardial artery and unimpaired flow.

For our discussion several terms should be defined. *Patency* – expressed as TIMI flow, denotes the percent of coronary arteries to be open at the time of angiography; *reflow* – represents the existence of blood flow in epicardial arteries beyond a patent stenosis; and *reperfusion* – the goal of the therapy, implies nutrient blood flow at the tissue level. The gold standard test for the success or failure of thrombolytic therapy is considered to be coronary angiography [7–9]. However, such an examination represents a "snapshot" of the coronary epicardial tree at a given moment, and cannot describe the dynamic changes that take place over time in the infarct-related artery and the myocardium supplied by the artery.

In light of these facts, a search for a reliable, non-invasive marker was begun. Chest pain resolution and biochemical markers failed to satisfy the clinical necessities. ST segment elevation resolution represents one of the most widely available and inexpensive markers for assessing the success or failure of reperfusion (thrombolytic or angioplastic) therapy.

In 1909 Eppinger and Rotenberg [10] observed ST segment elevations in dogs with experimental ventricular injury, and in 1920 Pardee [11] published his description of ST segment elevation as a clinical sign of coronary obstruction. More than 80 years have passed since these observations, yet the exact mechanism is still a subject of debate.

Myocardial cells during the early phase of repolarization carry the same transmembrane potential. Therefore they will not have any net current flow at the time the ST segment is inscribed. ST segment elevation from myocardial ischemia is caused by abnormal current flow (current of injury) between the boundary of normal and ischemic zones. Both diastolic and systolic injury currents have been invoked to explain the ST segment elevation [12].

Recently, various studies have suggested that ST segment elevation is related to the activation of sarcolemmal ATP-sensitive potassium (K_{ATP}) channels by ischemic ATP depletion. Li et al. [13] studied mice with homozygous knockout of the *Kir6.2* gene, which encodes the pore-forming unit of cardiac K_{ATP} channels. In the presence of left anterior descending artery ligation, while the ST segment elevation was evident in normal mice the elevation was absent in those with the knockout, supporting the concept that the K_{ATP} channels are responsible for ST segment elevation.

Throughout a long list of studies, two sets of cut-off points have been defined for the percent of STSER. The first has a cut-off point at 50% of the peak, or sum of peaks, of ST segment elevation magnitude in the significant(s) lead(s), and a two-domain set; STSER was considered when the magnitude resolved more than the cut-off point [14–19]. The second, used by other authors [20–23], is a three-domain set with cut-off points at 30% and 70%. No STSER was considered when ST segment elevation magnitude resolved below the first cut-off point, partial resolution if resolved between 30% and 70%, and complete resolution if resolved more than 70%.

Failure of thrombolytic therapy may be due to mechanisms acting at the site of original obstruction or at the level of the microvasculature. Several mechanisms have been proposed for failed thrombolysis in the epicardial artery, such as occlusion primarily due to plaque extension, raised levels of thrombin/antithrombin-III complexes [24,25], and, less certain, antibodies to streptokinase [26,27] and raised levels of lipoprotein(a) [28]. Failure at the microvasculature level is thought to be due to capillary occlusion with platelet microthrombi ("early no-reflow") and later by loss of microvascular integrity due to endothelial and myocardial edema ("late no-reflow"). In view of these facts, it is obvious that an angiography examination showing a patent IRA is not equivalent to reperfusion of the injured myocardium.

A number of studies compared the prognostic value of STSER with coronary angiography results after thrombolytic therapy. de Lemos and colleagues [20] observed that patients with complete

STSER = ST segment elevation resolution
IRA = infarct-related artery

(>70%) STSER from baseline at 90 minutes had a 94% probability of IRA patency (TIMI-2 or 3), a TIMI-3 flow rate of 79%, and 30 day cardiac mortality as low as 1%. Patients with partial (30–70%) STSER had 72% patent IRA and a TIMI-3 flow rate of 50%. Thirty day mortality in this group was 4.2%. Cases with no (<30%) STSER presented with 68% patent IRA and 44% TIMI-3 flow rate, while the 30 day mortality was 5.9%. Other studies, such as GISSI, found that two-thirds of the patients had complete (>50%) STSER 4 hours after thrombolysis, and 30 day cardiac mortality of 3.5% versus 5.7% in those without resolution. Schroder et al. [22] studied the prognostic power of early STSER 3 hours after the start of thrombolysis in patients recruited in the Intravenous Streptokinase in Myocardial Infarction Study. Complete (>70%) resolution was observed in 45%, partial resolution (70–30%) in 31% and no resolution in 24%. For the three groups, infarct size (measured by CK-MB percent release), echographic left ventricular ejection fraction 1 month after the event, and mortality rates at 21 days (2.2%, 3.4%, and 8.6%) were assessed. The authors concluded that no STSER was the most powerful independent predictor of early mortality. The mortality rates at 30 days were also comparable in a substudy of the Hirudin for Improvement of Thrombolysis (HIT)-4 Study.

It is worth mentioning here the results of research in which STSER was studied after primary percutaneous transluminal coronary angioplasty. In the Zwolle Angioplasty Study [29], all patients attained patent IRA with TIMI-3 flow, yet complete (>70%) STSER was seen in 51% patients, partial (30–70%) in 34%, and 15% had no (<30%) STSER. Matetzky et al. [30] examined the STSER of 117 patients after successful (TIMI-3 flow) angioplastic reperfusion for acute myocardial infarction. Seventy-six percent of the patients had complete (>50%) STSER while 24% did not. The group of patients without STSER was associated with high in-hospital (11% vs. 2%) and long-term mortality (21% vs. 12%), as well as with worse pre-discharge and late left ventricular ejection fraction. Such results support the theory that myocardial reperfusion requires patent IRA and an intact microvascular bed, and that STSER is a marker of myocardial reperfusion and not just of coronary artery patency.

Several investigators recently reported that persistent ST segment elevation is predictive of poor ventricular recovery and mortality. Andrews and co-workers [15] demonstrated that patients with complete (>50%) STSER and TIMI-2 or 3 on angiography presented with improved wall motion 48 hours after thrombolytic therapy, while those without STSER had worse wall motion. Van 't Hof [29], Somitsu [31] and Santoro [32] and their teams reached comparable conclusions, and the hypothesis was supported by results from contrast echocardiography [33] and nuclear scintigraphy [34].

Several studies demonstrated differences in STSER rates between anterior and inferior wall myocardial infarction. The authors of the TIMI-14 substudy as well as those of the HIT-4 substudy described improved STSER and better survival rates in patients with inferior wall infarction than those with anterior wall infarction. Because the J point is more frequently elevated in anterior precordial leads in normal and pathologic states, a systematic underestimation of STSER could occur in patients with anterior infarction. Furthermore, since anterior infarction is associated with larger infarct size, more extensive microvascular and tissue injury would be expected [20].

The large majority of studies defined success or failure of thrombolysis based on ST deviation analysis at 90 minutes from the start of therapy. The main principle was to reserve sufficient time for an invasive intervention if fibrinolysis was unsuccessful, in order to generate reflow to the jeopardized myocardium. In the HIT-4 substudy [21] mentioned earlier, Schroder et al. compared the prognostic value of STSER at 90 and 180 minutes after the start of thrombolytic therapy. They demonstrated advantages in delaying analysis for thrombolysis success/failure to 180 minutes, improving stratification of high versus low risk groups while preserving enough time for rescue PTCA. Complete STSER at 180 minutes identified 50% of the patients with a 30 day cardiac mortality less than 2% and was the most powerful independent predictor of early cardiac mortality in multivariate analysis. While mortality rates doubled at 180 minutes, the proportion of patients with no STSER decreased by two-thirds from 90 to 180 minutes. Those observations are consistent with recanalization of IRA later than 90 minutes after the start of streptokinase therapy. In contrast, de Lemos and co-workers [35] reported that patients with complete, versus those without, STSER at 60 minutes are likely to present with even lower risk for mortality and congestive heart failure. Nonetheless, such an early analysis will facilitate a more rapid decision about rescue PTCA.

Another point of controversy between two aspects of STSER is continuous versus "snapshot" ST segment monitoring. As noted earlier, angiographically defined patency provides only a brief anatomic visualization of the IRA. More prolonged angiography has shown that unstable patency is common. In several studies it was observed that the results of continuous ST segment monitoring and analysis for 90 to 360 minutes parallel cyclic flow changes in the culprit artery, permitting detection of coronary occlusion with a specificity of 90% and sensitivity of 64% [18] to 92% [19]. Shah et al. [16] demonstrated that a rapid and stable STSER pattern was an independent predictor for combined mortality or congestive heart failure whereas the TIMI flow grade was not.

In conclusion, over the years a number of bedside clinical markers were proposed for coronary artery patency and myocardial reperfusion after thrombolytic or angioplastic therapy. ST segment resolution was found to be the most reliable, due to its capability to bring to light infarction-related artery patency as well as nutrient blood flow at the myocyte level. Supplemental studies are required to elucidate divergences in different aspects, as mentioned earlier.

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PTCA = percutaneous transluminal coronary angioplasty

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