Early myocardial reperfusion: an assessment of current strategies in acute myocardial infarction

E. J. Topol

Department of Cardiology and the Joseph J. Jacobs Center for Thrombosis and Vascular Biology, Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

Early, complete, and sustained myocardial reperfusion is the principal goal of thrombolytic therapy. Unfortunately, the majority of patients treated today experience substantial delay before the initiation of thrombolytic therapy and, once treated, demonstrate suboptimal results of coronary thrombolysis. This is attributable, in part, to the underlying thrombus, which is platelet rich and resistant to plasminogen activators, and to the pro-thrombotic effects of fibrinolitics, which have no favourable effect on thrombin. Future therapeutic interventions will focus on improved reperfusion. Pharmacological strategies including novel plasminogen activators, direct thrombin inhibitors, and platelet glycoprotein IIb/IIIa inhibitors have all generated encouraging early clinical trial data and await further study. Mechanical reperfusion therapy with primary balloon angioplasty is particularly effective; its use is associated with the establishment of more complete infarct vessel patency than are thrombolitics. Considerable potential for the improvement of current reperfusion-directed therapy exists.

Key Words: Acute myocardial infarction, myocardial reperfusion, thrombolysis, coronary thrombosis, angioplasty, thrombin inhibitors, platelet aggregation.

Introduction

Until 1993, there had been considerable controversy regarding the importance of early, complete, and sustained reperfusion in the setting of acute myocardial infarction (AMI). The Global Utilization of Streptokinase and t-PA (tissue plasminogen activator) for Occluded Coronary Arteries (GUSTO) trial was specifically designed to evaluate the link between infarct vessel patency and clinical outcomes [1,2]. Its major finding was that the most important treatment determinant of survival and outcomes was early and complete reperfusion as assessed 90 min after initiation of thrombolytic therapy. However, only 54% of patients achieved this therapeutic goal, even with the most aggressive strategy tested [3]. This suggests considerable potential for more optimal reperfusion therapy in nearly half of patients: such therapy may be achieved by utilizing improved pharmacological agents or mechanical alternatives. In this article, the data substantiating the importance of complete and early reperfusion will be reviewed, the pathophysiological obstacles to improved reperfusion will be discussed, and the new approaches that are currently or will soon undergo evaluation will be presented.

Early and complete reperfusion

In the GUSTO trial, 41,021 patients with evolving AMI presenting for treatment within 6 h of symptom onset were randomly assigned to four different thrombolytic strategies. The primary end-point was all-cause 30-day mortality. A mechanistic substudy was included in the trial design to determine the role of infarct vessel patency in predicting outcome. In the angiographic trial, 2431 patients underwent coronary angiography at different pre-assigned (by randomization) time points. The investigators hypothesized that the earliest assessment — at 90 min after initiation of thrombolytic therapy — would correlate with clinical outcomes. A total of 1210 patients had coronary angiography performed at the 90-min point; the results of patency and mortality are summarized in Fig. 1. As shown, accelerated administration of t-PA was associated with the lowest mortality at 30 days (6.3%) and the highest infarct vessel patency (81%). Of particular note, the rate of complete infarct vessel patency, as assessed semiquantitatively by use of the Thrombolysis in Myocardial Infarction (TIMI) [3] scoring system, was 54% at 90 min. This represented about a 70% improvement compared with either of the streptokinase treatment arms (TIMI perfusion grade 3 flow rates of 29% and 32% for streptokinase with subcutaneous heparin and streptokinase with intravenous heparin, respectively).
Quantification of the link between patency and survival is an outgrowth of the trial\(^{[4]}\). The predicted and observed 30 day mortality rates for each of the four thrombolytic strategies are very close, and the proportion of squared error explained \( (R^2) \) was extremely high at 0.92 (Fig. 2). That is, once the extent of infarct vessel patency early after AMI is known, outcome may be predicted. Importantly, TIMI grade 3 flow emerged as the key parameter of treatment correlated with improved survival. Prior studies of infarct vessel patency had combined TIMI grades 2 and 3; only recently, coupled angiographic and clinical outcome measurements have documented that TIMI grade 2 flow is not associated with favourable clinical outcomes\(^{[4-6]}\).

It is also helpful to put this angiographic finding in perspective. Lee et al. have studied the clinical determinants of mortality in the GUSTO trial cohort\(^{[7]}\). The five factors determined to be most critical for affecting survival were age, low systolic blood pressure, advanced Killip class, elevated heart rate, and anterior location of the infarction. Collectively, these parameters constituted 90% of the prognostic information contained in the clinical baseline data. Whereas treatment was an independent predictive factor of outcome, its prognostic
input was far less (approximately 10% that of location of infarct) than the five major clinical determinants. Essentially, the health of the patient with respect to age, haemodynamic factors, and location of the infarct are paramount features. As improved reperfusion therapies are developed, it is worthwhile to bear in mind that the baseline clinical characteristics cannot be altered.

From the GUSTO trial data, if 100% TIMI 3 flow were achieved, the resultant 30-day mortality would be 4-0%. The fixed lower end of 4-0% mortality for thrombolytic-eligible patients is an index of the clinical risk features that operate independently of whether reperfusion is achieved. Some data on primary percutaneous transluminal coronary angioplasty (PTCA) for AMI suggest that very low mortality, perhaps even lower than 4-0%, can be achieved[2-10]. In the randomized trials comparing intravenous thrombolytic therapy with primary balloon angioplasty for AMI[8-13], the mortality associated with PTCA has approximated 2-9% (Table 1). Interestingly, the early complete reperfusion rate (TIMI 3 flow) achieved via mechanical dilatation of the infarct vessel is >90% — substantially better than with current pharmacological approaches.

It is unclear whether the very low mortality in the primary PTCA trials simply reflects better early reperfusion and less reocclusion or reinfarction, or whether the relatively small size of the trials and patient selection factors could have played a role in favourably skewing the data. Can the mortality associated with AMI be diminished to <3% with primary angioplasty? Such an improvement would clearly signify a major advance in the effectiveness of reperfusion strategies. This critical question is currently being examined in the second GUSTO trial (GUSTO-II), which is comparing alteplase with primary PTCA. GUSTO-II is the largest such trial to date with 10,000 patients enrolled; its data will be available in 1996.

With pharmacological or mechanical reperfusion strategies, the goal is complete reperfusion as soon as possible. The central issue — the timelines of therapy — is particularly highlighted by pre-hospital trials of thrombolytic therapy. Cumulative meta-analysis of the randomized trials[14-18] reveals a 15% reduction in 30-day all-cause mortality for pre-hospital compared with in-hospital initiation of therapy (Fig. 3). This coincides with the 15% reduction in mortality with front-loaded alteplase (t-PA) demonstrated in the first GUSTO trial[11]. Overall, the mortality results of the pre-hospital trials (related to savings of 1 h from symptom onset to treatment) and of accelerated regimens of t-PA (due to a reduction in time to achieving fibrinolysis by ≈1 h) emphasize the value of time in the setting of myocardial reperfusion. Unfortunately, the time elapsed between entry into the emergency room for evaluation of chest discomfort and initiation of thrombolytic therapy or primary angioplasty is still at least 60 min in most hospitals in the U.S.A.[19].

Obstacles to early reperfusion

Achieving successful coronary thrombolysis is a much more formidable therapeutic challenge than was initially envisioned. The underlying pathophysiology of plaque rupture is partly responsible. When the atherosclerotic plaque undergoes a fissure, with attendant exposure of subendothelial matrix, there is marked activation of platelets. The nidus of a coronary thrombus is a platelet aggregate, and platelets release not only vasoactive amines such as serotonin and thromboxane A2, but also plasminogen activator inhibitor (PAI-1). Thus, two components of the thrombus are intrinsically resistant to thrombolysis via plasminogen activators. Furthermore, the fibrin-rich thrombus — formed after the initial platelet aggregation and flow stagnation — is yet another source of resistance. Since the thrombus is composed of fibrin and thrombin, and plasminogen activators produce only fibrinolysis, a result of fibrinolytic use is the generation of free thrombin. This is a major underlying mechanism of the paradoxical pro-thrombotic effect of fibrinolytic therapy; the effects of thrombin are unleashed to autocatalyze more thrombin formation and induce platelet aggregation.
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effective thrombolysis, the rate of TIMI 3 flow
would fall to below 40% for current thrombolytic
strategies20,21.
These rates of coronary artery patency are estab-
lished by angiography, which provides a limited window
into the steady state and dynamics of coronary blood
flow. During typical angiography, infarct vessel patency
is assessed over the course of only a few minutes. In
contrast, continuous 3- or 12-lead electrocardiography
following coronary thrombolysis has revealed a com-
mon phenomenon called ‘intermittent patency’22,23.
About one third of treated patients exhibit this pattern,
described as fluctuations of ST-segment elevation in the
leads associated with the infarct region. Such electrocar-
diographic changes can be quite marked; although they
may be unaccompanied by symptoms of chest discom-
fort, these repetitive ST-segment elevations have been
validated and correlated with curtailment of coronary
artery blood flow22,23. The underlying cause of intermit-
tent patency remains unclear: it may be increased vascu-
lar tone from the release of thromboxane A2 and
serotonin, the release of thrombin after clot dissolution,
or both. The lack of symptoms associated with many of
the episodes may relate to partial denervation of cardiac
muscle resulting from the ischaemic insult, use of anal-
gesic medications, extensive myocardial damage, or
clouding of the clinical evaluation by the persistent chest
discomfort typically experienced for many hours follow-
ing initial presentation. Nevertheless, patients who dem-
strate this pattern of intermittent patency appear to
be at increased risk for reocclusion and reinfarction.
Early and complete infarct vessel patency must
be sustained to maintain myocardial salvage and
promote favourable left ventricular remodelling24,25.
Unfortunately, reocclusion is still a major obstacle,
occuring in approximately 8–12% of patients before
hospital discharge20,29 and during 1 year follow-up in
another 15–25% of patients27–29. The fate of patients
in whom infarct vessel reocclusion develops has been
shown to be markedly compromised, with a 2.5-fold
increased risk of death and, as expected, significantly less
recovery of left ventricular function30. Thus, durable
patency remains a critical and as yet unachieved objec-
tive of current thrombolytic regimens that include a
plasminogen activator, intravenous heparin, and aspirin.
For many years, cardiologists have interpreted
angiograms as being reflective of myocardial perfusion.
This has proved not to be the case. Using both angiog-
raphy and contrast echocardiography to evaluate reper-
fusion soon after thrombolysis, Ito and colleagues31
were the first to show that nearly 25% of their series of
patients had evidence of epicardial vessel filling and
clearance of dye; however, these suggestions of reper-
fusion were not accompanied by coronary blood flow at
the tissue level. Although the ‘no-reflow’ phenomenon
has been appreciated in the experimental laboratory for
many years, this investigation provided the first confir-
mation that it is a frequent clinical occurrence as well.
Agents that promote tissue level perfusion by blocking
white cell aggregation (or other mediators of reperfu-
sion injury sequelae) may improve tissue perfusion to
 correlate with restoration of epicardial blood flow.

**Figure 3** Reduction of mortality with pre-hospital administration of thrombolytic therapy. The results of five trials demonstrated an overall 17% risk reduction in cardiac mortality for pre-admission therapy compared with in-hospital initiation of treatment. APSAC = anisoylated plasminogen streptokinase activator complex (anistreplase); EMIP = European Myocardial Infarction Project Group; GREAT = Grampian Region Early Anistreplase Trial; MITI = Myocardial Infarction Triage and Intervention Project; RR = relative risk; UA = urokinase. Other abbreviations as in Fig. 1. (Adapted with permission from EMIP20.)

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Cellular and biochemical resistance to coronary
thrombolysis is reflected in the rates of rapid and
complete myocardial reperfusion. As already noted, in
the GUSTO trial, the TIMI 3 flow rate associated with
the most effective strategy (front-loaded alteplase) was
only 54% at 90 min after initiation of therapy. Much
higher rates achieved much faster are desirable. If
60 min was used as the time parameter for defining
effective thrombolysis, the rate of TIMI 3 flow
would fall to below 40% for current thrombolytic
strategies20,21.

The results of five trials demonstrated an overall 17% risk reduction in cardiac mortality for pre-admission therapy compared with in-hospital initiation of treatment. APSAC = anisoylated plasminogen streptokinase activator complex (anistreplase); EMIP = European Myocardial Infarction Project Group; GREAT = Grampian Region Early Anistreplase Trial; MITI = Myocardial Infarction Triage and Intervention Project; RR = relative risk; UA = urokinase. Other abbreviations as in Fig. 1. (Adapted with permission from EMIP20.)
Another explanation for reduced blood flow in the setting of reperfusion, particularly on a chronic basis after infarction, is the effect of residual stenosis. Even after a clot has been effectively dissolved, the high-grade residual stenosis that frequently persists may play a role in restricting coronary blood flow. Leung and Lau found that the presence of a significant residual stenosis was associated with ventricular dilatation during 1-year follow-up. This may, in part, explain the favourable long-term data published thus far on primary angioplasty for MI, since PTCA also addresses residual stenosis. In aggregate, the features of clot resistance, intermittent patency, reocclusion, and lack of perfusion are features that frequently affect the short- and long-term success of thrombolytic therapy — obstacles that must be fully addressed by therapeutic advances (Fig. 4).

**Future directions**

**Improved plasminogen activators**

A few distinct pathways are being explored in an effort to overcome several of the obstacles associated with contemporary reperfusion therapy. In the first of these, improved plasminogen activators may more efficiently lyse coronary artery thrombi via faster, more complete effects. Five 'third generation' plasminogen activators are in development, including reteplase (r-PA, Boehringer Mannheim, Mannheim, Germany), novel plasminogen activator (n-PA, Genetics Institute, Cambridge, Massachusetts), TNK (Genentech, South San Francisco, California), vampire bat plasminogen activator (Schering AG, Berlin, Germany), and recombinant staphylokinase (developed at Catholic University, Leuven, Belgium).

Of these new agents, all can be given in a single or double bolus intravenous injection regimen, a convenience compared to the infusion administration of the accelerated t-PA or streptokinase regimens. Clinical investigation thus far is most thorough regarding reteplase, a deletion mutant of t-PA, which is missing the finger, epidermal growth factor, and kringle-1 domains of wild type t-PA. Reteplase has been studied in a series of angiographic trials in Europe and the United States and was shown to achieve high patency at 60 min after initiation of therapy, a significant improvement over patency obtained with alteplase. The dose of reteplase is fixed at two boluses of 10 MU given 30 min apart. In the recently completed International Joint Efficacy Comparison of Thrombolitics (INJECT) trial performed in Europe, 6010 patients with AMI were randomized to therapy with reteplase or streptokinase within 12 h of symptom onset. Both groups of patients received intravenous heparin and aspirin. The patients receiving reteplase within 12 h of symptom onset had a slightly lower mortality at 35 days than those receiving streptokinase (9.0% vs 9.5%); this was not statistically significant. Similar to the findings of t-PA use compared with that of streptokinase, an excess of haemorrhagic strokes was associated with reteplase use compared with streptokinase (0.77% vs 0.37%, respectively). There was no significant difference, however, in total in-hospital strokes in the reteplase-treated group compared to the streptokinase-treated group (1.23% vs 1.00%, respectively). Whereas these clinical and angiographic findings collectively suggest that reteplase is a better thrombolytic than streptokinase, the INJECT trial was not adequately powered to validate superiority; it was set up to be an 'equivalence' trial. Currently, another large-scale trial with reteplase — GUSTO-III — has been initiated. In this
trial, 15,000 patients with evolving MI who present within 6 h of symptom onset will be randomly assigned to receive reteplase or front-loaded alteplase. Although the other new plasminogen activators have been studied in only a limited number of patients, all show promise to be more potent than wild type t-PA. Eventually, large-scale comparative trials will be necessary to prove their advantage. Of interest, three of the agents (staphylokinase, TNK, and bat-PA) demonstrate marked fibrin selectivity with only minimal breakdown of fibrinogen at doses that are efficacious in lysing coronary thrombi. It is uncertain, however, whether this feature will be linked to an excess of intracerebral haemorrhage or will potentially be responsible for a higher incidence of rethrombosis.

**Thrombin inhibition**

A second pathway to explore for facilitation of coronary artery thrombolysis is more effective thrombin inhibition. As already discussed, thrombin represents a key aspect of the resistance to clot lysis, driving platelet aggregation and the coagulation cascade in a prothrombotic direction, particularly following thrombolytic therapy. Heparin (conventionally used as the antithrombin anticoagulant) does not bind to clot-bound thrombin, requires antithrombin III as a cofactor, and is inactivated by platelet factor 4 and plasma proteinases.

The prototypical direct thrombin inhibitor is recombinant hirudin, the most potent known, naturally occurring anticoagulant. It binds to thrombin directly, including clot-bound thrombin. With encouraging results in pilot studies on facilitating coronary thrombolysis, hirudin is being tested in two large-scale trials (TIMI-9 and GUSTO-II), with results expected in 1996. The dose of hirudin had to be decreased with thrombolytic therapy; however, in the near future several Mb/Mb antagonists will be tested in clinical trials of thrombolysis because of a high rate of intracerebral haemorrhage and or will potentially be responsible for a mostly patent artery or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the TEAM-2 study. J Am Coll Cardiol 1992; 19: 1–10.

**Antagonism of platelet aggregation**

The third potential pathway, improved antagonism of platelet aggregation, represents an especially useful option. Advances in this area have become possible via the availability of platelet glycoprotein IIb/IIIa inhibitors, agents directed toward interference in the final common pathway of platelet aggregation. To date, only Integrin has been coadministered with thrombolytic therapy; however, in the near future several other IIb/IIIa antagonists will be tested in clinical trials of thrombolytic therapy.

The data for Integrin are supportive of a major effect in enhancing thrombolysis. In a consecutive series of 33 patients, the highest dose of Integrin tested (given in conjunction with an accelerated t-PA regimen), was associated with 85% of patients achieving TIMI 3 patency at 90 min after initiation of therapy and 100% patency if TIMI 2 and 3 flow were combined. No significant bleeding complications occurred. Large-scale trials are needed to confirm safety and to determine whether these initial encouraging results will be reflected in improved efficacy.

**Conclusion**

Despite considerable research efforts over the past decade, clinical investigation is still at an early stage in the development of myocardial reperfusion strategies. Now that it is abundantly clear that early restoration of complete TIMI 3 blood flow is essential and that reocclusion must be avoided, the therapeutic goals at the coronary arterial level are set. The obstacles to achieving better thrombolysis are largely understood at a pathophysiological level. In the years ahead, more effective strategies will undoubtedly be developed to further improve the prognosis of patients with AMI.

**References**


