‘Rescue’ after failed thrombolysis for acute myocardial infarction

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Summary

Prompt restoration of coronary artery patency in acute myocardial infarction is associated with substantial improvements in morbidity and mortality. The pivotal role of thrombolysis and aspirin in achieving these goals is well established. However, despite the success of thrombolytic therapy in large trials, clinical assessment in individual patients often suggests that reperfusion has not occurred after initial therapy. This review considers the validity of such bedside predictions and discusses whether such patients should be managed differently.

Keywords: acute myocardial infarction; thrombolysis; reperfusion; angioplasty

With the success of thrombolytic therapy in reducing mortality from myocardial infarction, has come an appreciation of its limitations. Increasing evidence links the initial objective of early, complete and sustained recanalisation of the infarct-related artery with improved outcome (figure); yet 90 minutes after the initiation of thrombolytic therapy only just over half of treated patients will have complete reperfusion.¹ Although many infarct arteries occluded at this time will go on to re-open spontaneously within a time window during

which benefit may still accrue, a substantial number of patients demonstrate suboptimal results from thrombolysis.

Against this background, admitting physicians on the coronary care unit frequently see patients in whom the clinical impression is of a failure to achieve early reperfusion. Can we really predict an adverse outcome? Should such individuals be managed differently?

Can we identify thrombolytic failure?

Salvage therapy for thrombolytic ‘failure’ is critically dependent on being able to identify confidently patients with persistently occluded arteries. Coronary angiography remains the reference standard for the diagnosis of reperfusion, but although the risks of arterial puncture in thrombolysed patients are not as great as might be imagined, logistic considerations preclude this as a routine approach. Furthermore, not only is reperfusion a dynamic process, but patency of the epicardial coronary artery may not accurately reflect tissue level perfusion – the ‘no-reflow’ phenomenon.² How accurate is the clinical impression of ‘thrombolytic failure’?

Although assays of a variety of circulating proteins, eg, creatine kinase isozymes, have been used to predict reperfusion in research studies, such assays are not in wide clinical use. The clinical impression is therefore typically based on two factors alone – persistence of chest pain and the surface electrocardiogram (ECG). Pain perception is subjective, and its intensity strongly influenced by analgesic drugs. It is perhaps unsurprising, therefore, that the persistence or resolution of symptoms does not have good predictive value in determining reperfusion status.³ The surface ECG best fulfils at least two of the essential criteria for a bedside marker of coronary patency, ie, ready availability and a minimum time penalty. Many investigators have assessed the ability of serial ECGs to predict the angiographic findings.^{4–8} Overall, such studies support the value of an early reduction in ST elevation in detecting reperfusion, with a sensitivity of 68–88% and specificity of 50–80% depending on the precise criteria used and the delay to angiography. The correlation between ECG change and angiographic outcome may be further enhanced by using continuous monitoring for ST trends rather than taking paired ECGs at arbitrary time points.^{9–10}

Figure Relationship between perfusion in the infarct related artery 90 minutes after thrombolytic therapy and mortality at 30 days. TIMI (Thrombolysis in Myocardial Infarction) grade 0–1 flow represents occlusion, grade 2 partial reperfusion, and grade 3 complete reperfusion. Mortality in patients with persistent occlusion of the infarct related artery is almost double that of patients achieving early TIMI 3 flow. (Data from GUSTO angiographic substudy¹)

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Equally importantly, a prompt reduction in ST segment shift appears to be associated with a better clinical outcome. In GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico), patients with >80% reduction in ST elevation 4 hours after the initiation of therapy had less than half the in-hospital mortality rate of those with <20% reduction,¹¹ while in ISAM (Intravenous Streptokinase in Acute Myocardial Infarction) early resolution of ST segment elevation was a powerful predictor of both early and late mortality after myocardial infarction.¹²

Although bedside monitoring may be inadequate to predict reperfusion status accurately in all patients, the evidence therefore suggests that some patients – perhaps those with a <20% reduction in ST elevation – may be correctly identified as having had an inadequate response to thrombolysis early in their clinical course. These patients represent a high-risk group who may benefit from more aggressive treatments, particularly if other markers of an adverse outcome (such as anterior location of infarction) are present.

Potential salvage strategies include mechanical revascularisation, principally coronary angioplasty, or repeat thrombolysis. Neither option is cheap or without risk, and any salvage strategy is inevitably subjected to a time delay which may diminish the possible benefits. Is there a place for such adjunctive therapy?

Coronary angioplasty

Large-scale clinical trials have clearly demonstrated that coronary angioplasty early after successful thrombolysis is unnecessary and possibly harmful. The position in patients in whom thrombolysis has failed to achieve reperfusion is less clear. Although coronary angioplasty early after thrombolysis carries particular difficulties, 80–90% of occluded arteries may be successfully re-opened in this setting.¹³ However, unsuccessful attempts at rescue angioplasty have been consistently associated with substantial mortality,¹³ and amongst the many reported studies of rescue angioplasty there have been only two randomised trials.

Of these, the study by Belenkie¹⁴ randomised only 28 patients and does not allow firm conclusions to be drawn. More recently, a larger study of 151 patients with first anterior myocardial infarction was reported,¹⁵ which relied on angiography to identify failure of thrombolysis. This trial showed a small reduction in the combined endpoint of death or severe heart failure at 30 days in the group undergoing intervention, but no change in resting indices of left ventricular function. Within this trial, technical success was achieved in 92% of patients, somewhat higher than in most other studies, probably reflecting the high levels of experience and expertise in the participating centres. Whether equivalent results could be obtained in less experienced institutions is open to debate. Conversely, the participating centres also represent the enthusiasts for an aggressive approach, and it is notable that patients entered into the study

Rationale for rescue therapy in acute myocardial infarction

- early patency of infarct-related artery only 55–85% with thrombolysis
- patent infarct-related artery confers survival advantage
- survival benefit may remain even when patency attained too late to influence ejection fraction

Box 1

registry but not randomised underwent angiography an average of 1.5 hours earlier, suggesting that many of the patients most likely to benefit from angioplasty may have been excluded. These caveats are the consequence of the inherent difficulties in conducting such a study and it is unlikely that better evidence will emerge in the near future.

It would therefore appear that urgent rescue angioplasty is likely to confer a benefit in some patients in whom the infarct-related artery remains occluded after thrombolysis. However, it also remains possible that equivalent (or greater) benefit could be obtained by delayed angioplasty to restore patency of the infarct-related artery, irrespective of the acute presentation, perhaps with less procedural risk. Although reperfusion after 3 hours does not generally result in recovery of systolic function, survival may still be improved by coronary artery patency after this time, through mechanisms such as decreased infarct expansion, enhanced electrical stability, and increased collateral flow.¹⁶

Rethrombolysis

The majority of myocardial infarctions are treated in centres without access to interventional facilities. Possible therapeutic approaches to increasing arterial patency in these centres include repeat thrombolysis with either the same or an alternative agent. Initial therapy with more than one thrombolytic agent in an attempt to improve reperfusion rate and maintain arterial patency has not been shown to improve outcome.¹⁷ Conversely, repeat thrombolysis for early recurrent ischaemia following successful reperfusion is of benefit.¹⁸ Is there evidence to support repeat thrombolysis where early reperfusion is not obtained?

Perhaps surprisingly, to date there are limited data with which to address this question. Rescue thrombolysis with intracoronary recombinant tissue plasminogen activator (rtPA) does appear to achieve high patency rates in patients with coronary thrombi initially resistant to streptokinase,¹⁹ but this must be set against the potential for spontaneous late reperfusion. In the only randomised trial of rescue thrombolysis with rtPA for patients with failed reperfusion as assessed by the surface ECG, Mounsey and colleagues showed a reduction in infarct size with rescue therapy, as assessed by ECG and gated radionuclide ventriculography.²⁰ This trial, however,

included only 37 patients in total, and the results should be interpreted cautiously. The placebo group received their initial thrombolysis with streptokinase later (although this did not achieve significance) and the second dose of thrombolysis was given approximately 6 hours after the onset of pain. It is widely accepted that limitation of infarct size in the majority of patients requires restoration of arterial patency within 2–3 hours, and it therefore seems improbable that the late restoration of arterial patency by rtPA could account for the results.

Current evidence thus appears inadequate to support a policy of routine repeat intravenous thrombolysis in patients whose ST segments fail to fall promptly following therapy, despite the intuitive attraction of such an approach.

Conclusion

What to do after thrombolytic 'failure' remains a contentious issue. Where clinical suspicion is high, and facilities and logistics permit, salvage angioplasty may have a role in selected patients. For the majority of patients with acute myocardial infarction, the imprecision of bedside markers of reperfusion and the uncertain benefit of repeat thrombolysis do not currently support a policy of repeat thrombolysis. Our efforts may be better directed at increasing the number of patients who survive to receive early thrombolysis, rather than pursuing marginal

Reperfusion strategies

Repeat thrombolysis

Advantages

- widely available
- less expensive

Disadvantages

- dependent on noninvasive markers of reperfusion with limited accuracy
- risk of bleeding
- no supporting evidence

Salvage angioplasty

Advantages

- angiographic evidence of failed reperfusion
- some supportive trial data

Disadvantages

- limited availability
- delay between diagnosis and intervention
- expense and logistics
- technically difficult
- adverse outcome if unsuccessful

Box 2

benefits in those who do not show an immediate clinical response. Nevertheless, to the clinician on the coronary care unit dealing with individual patients there will always be the feeling that some are being poorly served by the 'mega' trials on which we have come to depend – apparent thrombolytic failure is one issue which highlights this.

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