Clinical Perspective

How should we detect and manage failed thrombolysis?

Introduction

Trials of thrombolysis and primary angioplasty[1–5] have shown that coronary artery patency and the flow characteristics following thrombolytic therapy are important and independent prognostic predictors of outcome in acute myocardial infarction. From the thrombolytic trials it is clear that at least 30% of patients fail to recanalize 90–120 min after treatment[6]. It is also known that the prognosis of patients who do not reperfuse is worse than those who do[7–9]. Such conclusions are based on early angiography, although only a portion of these patients present with clinically obvious signs of continuing ischemia. Unlike primary angioplasty, which is accepted as a superior alternative to thrombolysis but underused for financial and logistic reasons, the role of diagnostic angiography and interventional therapy following failed thrombolysis is less than fully clear. Routine invasive investigation and interventional treatment seem to be neither practical (even in the U.S.A. only up to 12–20% of hospitals are equipped with diagnostic catheter facilities[10,11]), nor justified as indicated in earlier interventional trials[12]. Nevertheless, there is a substantial group of patients who fail to reperfuse after thrombolysis and who continue to show clinical signs of ongoing ischemia. How to best manage such patients is unclear.

How good is primary thrombolysis?

The size of the problem

A number of studies suggest that the best patency rates that can be achieved with currently available thrombolytic agents may be around 81%. TIMI III flow, which is the most important predictor of favourable outcome is, however, achieved only in 54% of patients[1–9]. How to detect failed reperfusion has been the focus of many studies. It is known from previously published data that, while there are markers which successfully predict reperfusion (such as complete resolution of chest pain and/or resolution of ST-T change), their absence is much less predictive for failed reperfusion[13]. Furthermore, outcome data suggest that, even at a more subtle level, resolution of ST-T changes may predict longer term outcome[6–9]. A true estimate of how many of these indicators of non-reperfusion are looked for in the thrombolized population is unavailable. In a U.K. survey among primary hospital physicians, estimates varied widely between 1 and 40%, with the majority of physicians suggesting that, in their opinion, 20–40% of thrombolized patients have signs of a failed reperfusion[15,16]. Many fewer physicians might be expected to fail to assess post-thrombolytic patients for evidence of reperfusion.

It is clear that reperfusion fails in a significant proportion of patients. What is less clear is whether outcome could be beneficially affected by additional reperfusion therapy. Even if proven to be effective, local circumstances may influence decision making about further treatment. Currently practice is based more on the availability of local facilities. Conservative management in the presence of failed reperfusion is more likely if a catheter laboratory is not available. In centres with interventional facilities it is sometimes regarded as ‘unethical not to intervene’ rather than basing a decision on whether to intervene on any evidence-based clinical trials. Thus, in the absence of good clinical data, it will always be likely that decisions will be based on predetermined impressions. In the U.K. survey the approach was evenly distributed between conservative management, further thrombolysis or percutaneous transluminal coronary angioplasty (PTCA)[15,16].

For the rational management of patients with failed thrombolysis the following questions need to be answered: How can we accurately and cost effectively detect non-invasively those who do not reperfuse after thrombolysis? If were able to identify such patients how should they be treated and when? Which is the best option: to do nothing, to repeat with a second thrombolytic intervention or to perform on-site or transfer for angiography and target lesion revascularization? If repeat thrombolysis is considered, would plasminogen activators, even
if given first time, be better than streptokinase? What is the role of the new antiplatelet agents, taking into account the promising results of TIMI 14 (alteplase + abciximab)\cite{17} and the fact that GUSTO IV (abciximab + reteplase for primary perfusion) has not even commenced? If PTCA is considered to be the best option, would the delay incurred in some patients, due to the need for transfer, negate any benefit? What impact would an invasive strategy have on the need for new facilities? Finally, would a combination of these strategies provide real additional benefit?

**Diagnosis of failed reperfusion**

Cessation of chest pain has been regarded as a clinically predictive sign of reperfusion, although it is very difficult to quantify for the purposes of a clinical trial\cite{18}. In one recent study only complete resolution of chest pain reasonably predicted successful reperfusion, although this sign was observed only in the minority of patients who were shown to have a patent target vessel (29%)\cite{13}. Analgesia, essential in clinical practice, will mask the presence of chest pain as a sign of failure of reperfusion. To suppress chest pain will result in failure to identify or delay treatment in some patients. The presence or absence of chest pain as a marker of reperfusion should be used in conjunction with other more objectively defined markers.

**Reperfusion arrhythmias**

Although frequently observed after thrombolysis as well as following primary PTCA, none of the observed arrhythmias (such as accelerated idioventricular rhythm) have been shown to add independent predictive information\cite{13}.

**Standard 12-lead ECG**

From a number of clinical trials it is clear that non-resolution of ST-segment changes after thrombolysis has predictive value for worse long-term outcome compared with resolution. Analyses assessing the acute predictive value of the ECG unfortunately predict successful perfusion rather better than failed reperfusion. There is a quantitative relationship between the degree of non-resolution and patency and an associated impact on short-term mortality prediction. Various authors have used a variety of ECG indices for reperfusion success or failure. They include 25% reduction in ST-segment elevation identified in the ‘worst’ lead on the post-thrombolytic ECG at 60–180 min post-thrombolysis, compared with the pre-thrombolytic ECG; the pre- to post-thrombolysis ECG of maximal ST-segment elevation ratio or the sums of the post-to pre-thrombolysis ST-segment elevation that is equal or less than 0·5. All have been described as having reasonable sensitivity and specificity, irrespective of the infarct site\cite{19,20}.

The GUSTO I study found that continuous ST-segment monitoring had good predictive value for non-reperfusion especially when there was more than 4 mm of initial ST-segment elevation\cite{21}. Continuous ST-segment monitoring has been shown to be promising in other studies, but clarification in larger trials is needed. While such equipment is generally not available in community hospitals at present, it may be argued that the additional cost of equipment for continuous ST-monitoring could be offset by the benefit of reliable stratification for further intervention, provided of course that further therapeutic strategies were proven to be effective.

**Biochemical markers**

**Markers of reperfusion/non-reperfusion**

Considerable interest exists in developing fast bedside diagnostic kits for early diagnosis of myocardial infarction, since 50% of infarcts can present without diagnostic ECG changes or an accompanying obvious clinical presentation. Whether thrombolytic treatment based on biochemical diagnosis alone would be beneficial is less clear. Of the numerous markers, creatine kinase isoenzyme, troponin T or I and myoglobin measurements are the most widely used. The rapid peaking of myoglobin seems to be the earliest marker of a successful recanalization, whilst the rate of troponin T rise over 3 h post-thrombolysis has revealed very high (94%) sensitivity as well as specificity (100%) in this situation\cite{22}. There is only limited evidence that any of these markers can predict failure to achieve TIMI 3 flow at 60–90 min with any degree of similar accuracy\cite{23,24}. Even though rapid assessment of myoglobin and kits for troponin for bedside diagnosis have recently become available, creatine kinase-MB assessment is still the marker most frequently used in community hospitals. At present these essays are mostly reserved for post hoc confirmation, rather than for direct decision, so that they may not help in the triage of patients with failed reperfusion. Early peaking of levels of these markers, while suggesting restoration of flow does not always mean achievement of reperfusion (e.g. presence of washout from recanalized arteries without reperfusion due to persistence of microvascular...
dysfunction). The failure of accuracy and interpretation makes their reliable use difficult in the setting of failed reperfusion, especially in the absence of concomitant ST-segment resolution\textsuperscript{[25]}.

**Biochemical assessment of a failure of achieving lytic state**

There is some evidence that patients who fail to achieve detectable fibrinogenolysis following thrombolysis could benefit from additional reperfusion treatment using additional thrombolysis. In one small study, benefit was confined to those patients whose fibrinogen remained at greater than 1 g. l\textsuperscript{-1} following therapy with streptokinase\textsuperscript{[26]}.

Although fibrinogen assay is not routinely tested, this measurement is potentially advantageous for distinguishing patients in whom non-reperfusion is primarily due to non-fibrinogenolysis rather than due to no reflow. In such cases it would suggest that further thrombolysis and/or intensified antiplatelet therapy rather than interventional treatment may be beneficial. The situation is more complicated than this, however, since the no-reflow phenomena can also be related to a prothrombotic effect of thrombotic therapy, which would suggest the need for further intensified antiplatelet therapy rather than interventional treatment\textsuperscript{[27,28]}.

Fibrinogenolysis itself can have a prothrombotic effect by exposing free thrombin and facilitating platelet aggregation which then promotes further thrombus formation despite facilitation of further fibrinogenolysis with thrombolitics. Failure to achieve a lytic state can then be related to platelet aggregation rather than to inadequate fibrinogenolysis. Routine laboratory monitoring of platelet function may become necessary with the advent of new drugs with potent selective antiplatelet action. Sensitive tests of platelet activation such as flow cytometry are unlikely ever to be applicable in routine clinical practice.

**Emerging diagnostic strategies**

Even though SestaMIBI has good accuracy in assessing patency after systemic thrombolysis, the need to obtain pre-thrombolytic scans precludes this method from wide clinical application\textsuperscript{[29]}. The acute assessment of microvascular perfusion by myocardial contrast echocardiography may be the most promising strategy\textsuperscript{[30]}. Contrast agents are currently being tested in pre-clinical trials and should become available for clinical trial assessment use in about a year\textsuperscript{[31]}.

**Summary**

In routine clinical practice, careful careful observation of patient symptoms, with frequent clinical assessment and determination of whether there is resolution of 12-lead ECG at 90–120 min, seem to be a realistic strategy for assessing patients in whom reperfusion has failed. Such patients could then be considered for further thrombolysis or intervention. The situation may well change if newer targeted antiplatelet therapy is shown to be effective, in which case more detailed platelet function monitoring for tailoring of subsequent therapy may become necessary.

**What to do about apparent failed thrombolysis**

**Further thrombolysis**

Although further thrombolysis is not infrequently used in routine clinical practice, there is only limited evidence available to support the strategy. Lack of proven benefit is surprising, considering the potentially large impact such available therapy could have in most hospitals. While White et al. and Verheugt et al. showed benefit in opening the infarct related artery with intracoronary\textsuperscript{[22]} or systemic\textsuperscript{[30]} tPA following failure with systemic streptokinase, their investigations were made in non-randomized trials. Mounsey et al.\textsuperscript{[26]} showed in a small group of patients (stratified on the basis of 25% non-resolution of the ECG) that there was benefit with additional intravenous alteplase in terms of improvement in left ventricular ejection fraction at 6 weeks. The only other available data are observational\textsuperscript{[34]}.

Pathophysiologic studies (activation of platelets, exposure to thrombin, continued presence of disrupted plaque) fail to support the theoretical benefit of such repeated treatment. Moreover, there seems to be little benefit from repeating thrombolysis later (more than 6 h) rather than sooner, as the limited positive impact of late recanalization on reperfusion can be offset by a small but possibly deleterious effect of increased risk of bleeding\textsuperscript{[35]}.

A large trial would be needed to assess the effectiveness of repeated thrombolysis, but, in view of more recent advances in targeted antiplatelet therapy, the role of repeated thrombolysis may need to be redefined. The safety of antiplatelet combined with
thrombolytic therapy will be assessed in GUSTO IV. The previous higher rates of intracranial haemorrhage with combination treatments such as with hirudin (TIMI 9, GUSTO II, HIT 3) should, however, raise a cautionary note. Recent data on combining thrombolytic and antithrombins continue to suggest the therapeutic window is narrow.

**Additional antiplatelet therapy**

It is known from angiographic data of patients referred for rescue PTCA that there is a greater degree of no reflow phenomena compared with primary PTCA patients, suggesting additional microcirculation occlusion, probably due to platelet microthrombi[36,37]. Newer data showing a reduction in thrombotic events and better final flow characteristics in acute coronary syndromes with abciximab, indicate that this treatment could be potentially useful even outside coronary interventions, as has been shown in preliminary studies[38]. Concurrent use of both thrombolytic and glycoprotein IIb/IIIa inhibitors is being studied in clinical trials (GUSTO IV) and there is a prospect of developing joint strategies (antiplatelets plus thrombolytic) in future thrombolytic regimens. So far no clinical data is available regarding this strategy in ‘rescue’ settings. For its routine use we will also need information about its safety, especially with the potential risk of increased bleeding.

**Rescue PTCA**

Despite the widespread belief that something needs to be done in patients with clinical signs of failed reperfusion, little is known from trial data about the true value of the more costly rescue PTCA. To date only tens of patients were involved in prospective trials assessing the value of the strategy[39,40]. In the TIMI IV subgroup analysis no significant benefit was shown in the intervention group compared with conservative management[41]. However, Juliard et al. has shown rescue PTCA results that compare well with primary PTCA in the same hospital[42]. Analysis of the intervention subgroup of the GUSTO I substudy[27] has shown a trend towards superior left ventricular function and 30-day mortality in the PTCA group compared with the conservative strategy. The outcome of these patients was even less favourable however when compared with patients in whom initial thrombolysis was successful. Failed rescue PTCA in the setting of failed thrombolysis was a significant predictor of high mortality (30%). This study was not a randomized trial and had baseline discrepancies in different treatment groups, especially in left ventricular function. Analysis of the TAMI 5 study subgroups of patients with an occluded artery post-thrombolysis showed no benefit in patients who underwent early rather than pre-discharge PTCA[42]. The RESCUE trial compared 150 patients with late (8 h) signs of occlusion of left anterior descending artery post-thrombolysis[43], and although results suggested improvement in left ventricular ejection fraction and composite end-points, meta-analysis of above three trials does not indicate any overall mortality benefit.

The DANAMI I study[44] showed that patients who present late pre-select themselves to survive and that intervention in such patients may be beneficial. It is less clear whether benefit is obtained even when the patient is transferred for intervention to a referral cardiac centre, since this is still the most typical geographical situation in cardiac services in most European countries.

**Retrieval/salvage PTCA**

As is well known, patients treated with primary PTCA at an interventional centre derive benefit from primary PTCA compared with thrombolysis only when transfer, if necessary, can be expedited without delay[45,46]. Further evidence also suggest that after the first 2 h following acute myocardial infarction onset, the relative gain from PTCA intervention is larger compared with thrombolysis, probably due to the fact that reopening the artery positively affects other factors, rather than just myocardial salvage (prevention of left ventricular dilatation, prevention of electrical instability and providing a source of collateral flow[47]). There is a good deal of retrospective and audit data[48-50] suggesting that a ‘hub and spoke’ strategy with pre-selection of patients locally results in favourable short-term outcome in treated patients. No randomized data are available as yet and there are no comparable data available for patients who were managed conservatively locally. While patients with relatively late intervention (about 12 h), had angiographic success in more than 80% of cases (TIMI grade III achieved as result of rescue PTCA), many still had definite Q wave infarction on discharge and had significant peak creatine kinase levels. It is possible that patients for intervention were pre-selected and their outcome would be favourable even if treated conservatively. Comparison of outcome with matched patients randomized to the different treatments with a clear definition criteria for intervention is required before recommending this strategy for routine practice. If proven effective, however, the
strategy of sensible triage of patients, with the majority being thrombolized in local hospitals and those who fail to reperfuse being transferred to a cardiac centre, would be appear a reasonable strategy. The best of both worlds would thus be achieved, with local rapid cheap thrombolysis and improvement of outcome for those who fail to reperfuse, by transferring them for early intervention. Intervention in such a setting could contribute to the management of acute myocardial infarction in the community. At present primary PTCA has little impact on acute myocardial infarction treatment in the community, even in patients presenting in a centre with interventional facilities in the immediate referring area. Referring only patients with failed reperfusion to a cardiac centre for interventional treatment could probably be a realistic trade-off between additional expenses and resources and a significant contribution to cardiac care in the community. The question of the true merit of this approach is thus paramount, not least since such patients would represent only up to 5% of the total interventional workload in cardiac centres and could thus be easily accommodated without substantial additional need for funding of staff and equipment. Only a trial however would provide the clinical value, the cost/benefit and thus the burden on health care resources. A further question could arise. Would such patients be pre-treated with antiplatelet agent prior to and during transfer? Antiplatelet therapy so used seems to have a positive effect on the outcome of late PTCA[51]. Whether the active search for signs of failed reperfusion in the early stage of acute myocardial infarction is superior to the DANAMI strategy of initial conservative management with pre-discharge risk stratification and selection for late intervention remains to be seen.

Currently the large national U.K.-based study funded by the British Heart Foundation is about to start. The REACT (REscape Angioplasty versus Conservative management of Thrombolysis) proposes randomizing 1200 patients after thrombolysis into three groups: conservative treatment further thrombolysis, or referral for invasive investigation and treatment. The results of this study could have an impact on the management of acute myocardial infarction in the health care systems, where access to interventional cardiac services is restricted and primary PTCA is then not considered as a viable option. A further study in planning (REACT II) may evaluate the patients, who settle initially, but then redevelop further symptoms/ECG changes, rather than simply making a routine assessment at 90 min.

Until the results of this and similar studies are available, we can expect to continue the present selection based on bias and on the referring physician’s

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<th>Non-invasive diagnostics of failed thrombolysis</th>
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<tr>
<td>Non-resolution of chest pain</td>
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<td>ECG-non resolution of ST-T elevation (&lt;25–50% resolution at 60–180 min post-thrombolysis)</td>
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<td>Enzyme kinetics</td>
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<td>Troponin T or creatine kinase-MB mass or myoglobin ratio post-/pre-thrombolysis</td>
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<td>&lt;5 at 60 min</td>
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<td>&lt;10 at 90 min</td>
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<td>Myocardial contrast echocardiography</td>
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**Other intracoronary based interventions**

Preliminary evidence from small studies suggests that strategies such as intracoronary therapeutic ultrasound or thrombectomy could be useful in achieving lysis of intracoronary thrombus as well as promoting microvascular reperfusion[52–56]. There is good theoretical ground for their action which, if proven in clinical trials, could add to the present armamentarium as adjunctive procedures combined with PTCA and stenting.

**Reperfusion injury prevention**

At the moment, despite encouraging experimental data, there is little clinical evidence that the use of lipid peroxidase inhibitors influences clinical outcome[57–60].

**Intra-aortic balloon counterpulsation**

There is limited evidence that intra-aortic balloon counterpulsation can improve outcome in patients with failed thrombolysis, especially in a high-risk group of patients[61,62]. However, if the data from current trials is confirmed, this could present a ‘trade off’ with the possibility of instituting intra-aortic balloon counterpulsation in hospitals with the basic angiographic facility.

**Emerging/combined strategies**

With the advent of new potent targeted antiplatelet agents, there are some promising data suggesting that these could be very useful not only as a bail-out measure prior to and during intracoronary intervention but also as primary adjunctive treatment. In the
TIMI 14 study, thrombolysis was facilitated with a combination of reduced doses of alteplase and abciximab[17]. Data from the GRAPE study suggest that abciximab used in anticipation of further intervention could recanalize up to 40% of occluded vessels[63]. In GUSTO III there was better outcome in the rescue PTCA group if abciximab was used prior intervention[64]. It is possible that a combined approach using a combination of all reperfusing methods (thrombolysis, antiplatelet agents, intracoronary intervention) could offer the best reperfusion option.

Conclusion

Although failed thrombolysis still presents sizeable clinical problems, there is no proven therapeutic option that seems currently to be clearly superior to any other. In the absence of sound clinical data, all that can be recommended is careful, frequent assessment of the patient’s clinical status with frequent 12-lead ECG control (90–120 min at least) in order to form a basis for consideration for further thrombolysis or intervention, if this option is easily achievable.

In future it is likely that it will be shown that these patients comprise a heterogenous group with different levels of failed lysis, microvascular no reflow and/or different degrees of critical stenosis in the target vessel. Careful weighing of these factors in the individual patient will result in a more tailored approach.

If interventional strategies are shown to be superior, their implementation into community treatment of acute myocardial infarction will depend on whether the benefit is sustained, even after delays incurred in transferring patients to a neighbouring cardiac centre, and whether the extent of diagnoses demanded for these services can be realistically met within the existing health care resources. The results of large clinical trials undertaken during the early post-thrombolytic as well as during subsequent stages in patient stay are desperately needed.

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[14] ISIS 3 (third international study of infarct survival), Collaborative group. ISIS 3: a randomized trial of streptokinase vs tissue plasminogen activator vs antistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction. Lancet 1993; 342: 753–70.


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