Clinical markers of thrombolytic success

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Although a number of markers of successful coronary thrombolysis have been proposed, only a few of these have the two necessary features of a clinically useful marker: (1) widespread early availability and (2) good predictive value. The reduction in ST-segment elevation on the standard 12 lead electrocardiogram 1–4 h after initiation of thrombolysis may be the simplest and most useful clinical 'tool' to gauge the effectiveness of thrombolytic therapy. The predictive value of this single marker might be further improved by combining it with assessment of the rate of increase of serum myoglobin and of troponin T, provided these determinations were rapidly available.

Key Words: Acute myocardial infarction, thrombolysis, coronary recanalization, markers of reperfusion, ECG monitoring, serum myoglobin, troponin T.

Introduction

Prompt reestablishment of blood flow through an occluded coronary artery is the most important goal in the management of patients with acute myocardial infarction (AMI): compared with persistent occlusion, early patency of the infarct-related artery is associated with reduced mortality. Thrombolytic therapy is frequently followed by rapid recanalization of totally occluded coronary arteries and saves about 30 lives per 1000 patients receiving treatment within 6 h of the onset of symptoms.

In the recent Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) angiographic trial, following the early administration of thrombolytic therapy to unselected eligible patients with AMI, the average survivor had good left ventricular function with a mean ejection fraction of ≈57%. Because left ventricular function is among the most important determinants of prognosis, it is unlikely that new treatments will sizably improve overall outcome for these patients since their current level of ventricular function is associated with relatively low mortality. New treatments administered to unselected patients eligible for thrombolysis are therefore likely to yield, at best, only small additional survival benefits, and the trial of such agents would require treatment of many thousands of patients to achieve statistical significance.

Conversely, a cost-effective improvement of outcome might be obtainable in subgroups of patients with AMI who currently have an adverse prognosis. For example, even the most successful thrombolytic regimen tested in the GUSTO trial failed to obtain complete reperfusion (Thrombolysis in Myocardial Infarction degree of perfusion [TIMI] grade 3) after 90 min of therapy in as many as 46% of patients and, in this subgroup, 30-day mortality remained high (about 8.2% compared with only 4.4% in patients with complete reperfusion). Compared to current regimens, adjunctive therapies (such as direct thrombin inhibitors) may further increase the likelihood of early coronary artery recanalization; however, these treatments are associated with a greater incidence of haemorrhagic stroke and major bleeding (≈40 more major bleeds per 1000 patients occur with hirudin than with heparin). Thus, routine aggressive treatment in all patients with AMI is probably not cost-effective, especially in patients who would have achieved early and complete recanalization with standard therapy alone.

Invasive therapeutic strategies, such as routine angiography with percutaneous transluminal coronary angioplasty (PTCA) after thrombolytic therapy, have not been shown to have a beneficial effect on prognosis when administered to unselected patients: the results of many studies show a trend toward increased risk in the invasively treated group. In contrast, the results of two recent small trials suggest that angiography with PTCA seems beneficial when limited to patients at high risk who have evidence of failed reperfusion during thrombolysis. Similarly, the administration of additional antithrombotic agents only to patients with early unsuccessful thrombolysis might reduce the risk/benefit ratio of such adjunctive treatment.

For these reasons, early, accurate clinical markers of thrombolytic success are desirable. Such markers could indicate which patients are likely to benefit from selective use of additional interventions.
Prediction and detection of failed thrombolysis

The ideal marker of coronary reperfusion would predict when standard thrombolytic therapy will not lead to prompt coronary recanalization; thus, a more specific treatment (i.e. primary angioplasty or adjunctive antithrombotic agents) could be adopted immediately in such cases. Unfortunately, clinical and laboratory predictors of failed thrombolysis are scant since the mechanisms underlying acute coronary occlusion and the variable response to lytic therapy are still largely unknown. At present, we have at our disposal mainly markers of successful or failed reperfusion that inform us of the process only after it has occurred.

Searching for predictors of failed thrombolysis with standard therapy

A number of conditions have been associated with subsequent thrombolytic outcome. Most of these observations, however, provide only an approximation of the efficacy of thrombolytic therapy and are not predictive of outcome for an individual patient.

Pre-infarction angina

The results of a recent study suggest that patients with unstable angina in the 7 days before AMI have remarkably faster coronary recanalization during thrombolysis, as well as smaller infarcts, compared to patients with unheralded MI. The reasons for this different response are not clear.

Cigarette smoking

Surprisingly, smokers generally have a better response to thrombolytic therapy than non-smokers. A possible explanation may be that in smokers, the mechanism of infarction is more often thrombosis of a less critically stenosed coronary artery.

Circadian variation of thrombolytic efficacy

A circadian rhythm in the response to administration of recombinant tissue plasminogen activator and urokinase has been described. Significantly lower coronary recanalization rates occurred in the morning—when platelet and coagulation reactivity, blood viscosity, vasomotor tone, and the natural inhibition of fibrinolysis are at their highest—than during the remainder of the day.

Plasma levels of thrombin antithrombin III

The plasma concentration of thrombin antithrombin III complexes in peripheral venous blood drawn on admission has been found to be significantly greater in patients with subsequent unsuccessful thrombolysis than in patients with effective recanalization. An important limitation of such biochemical predictors of perfusion status, however, is the delay inherent in laboratory measurement that currently precludes rapid bedside use.

Thus far, no handy, reliable predictor can distinguish the response of patients to thrombolytic treatment at the time of hospital admission.

Markers of perfusion status

With the advent of the thrombolytic era, several markers of early reperfusion have been proposed, including the resolution of pain, the occurrence of arrhythmia, the reduction of ST-segment elevation, and several biochemical indices (Table 1).

Evolution of pain

Persistent chest pain, not alleviated by sublingual or intravenous nitrates, is a typical feature of AMI. It has been suggested that the sudden decrease of pain may indicate coronary reperfusion. The relationship between pain and myocardial ischaemia, however, is indirect and often elusive. Pain perception is subjective, and patients often continue to report pain hours after successful reperfusion. In addition, the intensity of pain is strongly influenced by analgesic drugs. Thus, the persistence of symptoms or the sudden and complete resolution of chest pain do not have a good predictive value in detecting the status of myocardial perfusion.

Arrhythmias

Arrhythmias are a specific marker of myocardial reperfusion in experimental models. In sharp contrast,
reperfusion arrhythmias are not common in patients with AMI, and there is no convincing evidence that ventricular arrhythmias (including idioventricular rhythm or slow ventricular tachycardia) occur more frequently in humans during successful coronary thrombolysis than during failed thrombolysis\textsuperscript{17,19,20}\textsuperscript{17,19,20}. (Fig. 2). The reasons for this striking difference between animal models and clinical evidence are complex and are not simply related to the sudden reperfusion of non-stenosed arteries in the experimental model since reperfusion

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**Table 1** Sensitivity and specificity of various markers of coronary recanalization

<table>
<thead>
<tr>
<th>Marker</th>
<th>Study</th>
<th>Cut-off</th>
<th>Time from initiation of thrombolysis</th>
<th>Time of angiography</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of ST elevation</td>
<td>Clemmensen\textsuperscript{(25)} (n = 56)</td>
<td>≥ 20% reduction</td>
<td>180 min</td>
<td>180 min</td>
<td>88%</td>
<td>80%</td>
</tr>
<tr>
<td>Sum of ST elevation</td>
<td>Barbash\textsuperscript{(26)} (n = 286)</td>
<td>≥ 50% reduction</td>
<td>60 min</td>
<td>72 h</td>
<td>87%</td>
<td>76%</td>
</tr>
<tr>
<td>Sum of ST elevation</td>
<td>Bossaert\textsuperscript{(27)} (n = 103)</td>
<td>≥ 50% reduction</td>
<td>240 min</td>
<td>10-12 days</td>
<td>73%</td>
<td>63%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Calif\textsuperscript{(17)} (n = 386)</td>
<td>Improvement</td>
<td>90 min</td>
<td>90 min</td>
<td>84%</td>
<td>29%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Calif\textsuperscript{(17)} (n = 386)</td>
<td>Resolution</td>
<td>90 min</td>
<td>90 min</td>
<td>34%</td>
<td>83%</td>
</tr>
<tr>
<td>CK-MB</td>
<td>Miyata\textsuperscript{(45)} (n = 63)</td>
<td>≥ 1-5-fold increase from baseline</td>
<td>15 min</td>
<td>Serial up to</td>
<td>44%</td>
<td>100%</td>
</tr>
<tr>
<td>CK-MB</td>
<td>Abe\textsuperscript{(38)} (n = 38)</td>
<td>&gt;25 IU·l\textsuperscript{-1} increase from baseline</td>
<td>60 min</td>
<td>Serial up to</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>CK-MM</td>
<td>Lapertche\textsuperscript{(38)} (n = 27)</td>
<td>MM3/MM1 ratio ≥0.35</td>
<td>60 min</td>
<td>90 min</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td>Troponin T</td>
<td>Abe\textsuperscript{(38)} (n = 38)</td>
<td>&gt;0.5 ng·ml\textsuperscript{-1} increase from baseline</td>
<td>60 min</td>
<td>Serial up to</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Miyata\textsuperscript{(45)} (n = 63)</td>
<td>≥ 2-fold increase from baseline</td>
<td>15 min</td>
<td>Serial up to</td>
<td>71%</td>
<td>100%</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Ellis\textsuperscript{(43)} (n = 42)</td>
<td>&gt;4-6-fold increase from baseline</td>
<td>120 min</td>
<td>Serial or up to</td>
<td>85%</td>
<td>100%</td>
</tr>
</tbody>
</table>

CK-MB, CK-MM = serum creatine kinase isoenzymes.
Reduction in ST-segment elevation

It is generally accepted that the resolution of ST-segment elevation may be a simple index of coronary recanalization. Early studies using intracoronary thrombolysis demonstrated a sudden decrease of the ST-segment shift after successful myocardial reperfusion[22,23]. Afterward, many investigators assessed the predictive value of serial 12 lead electrocardiograms (ECGs) in detecting angiographically documented recanalization[24-27]. Overall, these studies demonstrated the value of serial ECGs in detecting reperfusion: a 20-50% reduction in the sum of ST elevation was associated with a sensitivity of 73-88% and a specificity of 63-80% (Table 1).

The results of these small angiographic studies have been indirectly confirmed by the data of the large Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial, which showed that patients with a decrease ≥50% in the sum of ST elevation in all 12 leads at 4 h after initiation of thrombolytic therapy had a strikingly better short-term outcome[28]. The difference was even more impressive when patients with a >80% reduction in the ST shift were compared with those having a <20% reduction. The intermediate groups (20-80% reduction in the ST shift) showed only a small difference in mortality. The two extreme groups included about 54% of the study population (Fig. 3).

Similarly, the results of the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) trial showed that early (≤3 h) resolution of ST elevation was a powerful predictor of both early and 6-year mortality after AMI[29]. Thus, the presence or lack of rapid, persistent resolution of ST-segment elevation may correctly identify perfusion status in >50% of patients with AMI. Furthermore, this parameter is also a good marker of prognosis.

Dynamic changes in ST elevation

The dynamic evolution of AMI with intermittent ST elevation has been well described. This phenomenon may influence the assessment of recanalization through ECG criteria (Fig. 2)[30]. Recurrent ST elevation is associated with coronary reocclusion and a worse short-term outcome[31].

Continuous ECG (Holter) monitoring has been successfully used to identify intermittent ST elevation[32]. However, because Holter monitoring allows only retrospective analysis of the data, its use cannot influence real-time clinical management. Real-time computer assisted 12 lead ECG monitoring has been found to detect failure of reperfusion and to indicate which patients have recurrent ST elevation[33,34]. This technique, although not widely available, can also measure duration of ischaemia, which appears to be the most important determinant of infarct size[35].

Indices of myocardial necrosis

Successful reperfusion causes an earlier release of biochemical indices of myocardial necrosis into peripheral blood. On the basis of this principle, the serial measurement in serum or plasma of several markers of reperfusion has been proposed. Such markers include creatine kinase (CK), the CK-MB isoenzyme, troponin T, and myoglobin[34].
Immediate determinations of serum CK and CK-MB are usually available in the emergency laboratory. Peak values of serum CK and CK-MB beyond 12 h from initiation of thrombolysis are a well-known index of failed reperfusion (sensitivity 84%, specificity 95%), but only retrospectively\[(39)\]. Rates of increase of serum CK>50 IU·h\(^{-1}\) and of serum CK-MB >10 IU·h\(^{-1}\) over the first 2-5 h of treatment indicate successful thrombolysis\[(39)\] and may be more useful clinically. Similarly, a ≥2-5-fold increase in serum CK-MB concentration during the first 90 min of t-PA infusion was found to correlate with early coronary revascularization with considerable accuracy\[(37)\]. The value of a very early rate of rise of serum CK-MB level (within the first 15-60 min of thrombolysis) has also been investigated (Table 1). Finally, the determination of serum CK-MM isoforms — which requires a highly specialized laboratory — and their rate of increase can also provide an early (≤3 h) evaluation of reperfusion\[(38,39)\] (Table 1).

Similarly, recent studies have shown that a >0.5 ng·ml\(^{-1}\) rise of troponin T levels in the first 60 min of thrombolytic therapy may correctly identify successful reperfusion (Table 1)\[(40)\]. Although the current assay for troponin T requires at least 90 min\[(41)\], a whole-blood, rapid bedside device for troponin T measurement within 20 min has just become commercially available; its sensitivity and specificity appear to be comparable to the traditional assay\[(42)\].

Myoglobin is a sensitive, although non-specific, marker of myocardial necrosis. A peak serum concentration ≤3-5 h after initiation of lytic therapy gives an accurate, albeit retrospective, prediction of early coronary reperfusion\[(43)\]. A ≥4-6-fold increase in the first 2 h after lytic therapy can also signify reperfusion (sensitivity 85%, specificity 100%)\[(44)\] (Table 1). Moreover, the rate of rise of serum myoglobin level within the first 15 min after initiation of thrombolysis has been found to indicate reperfusion with a better accuracy than the rate of increase of serum CK-MB\[(45)\]. Unfortunately, since myoglobin is rapidly released from the necrotic myocardium even before thrombolytic therapy, myoglobin is not a good marker of reperfusion in patients treated >4 h after the onset of symptoms\[(46)\] and in patients with early intermittent spontaneous reperfusion\[(47)\].

Although these biochemical markers of reperfusion have, overall, a good predictive value for detecting perfusion status, their results are influenced by the presence of collateral circulation and of intermittent reperfusion. Furthermore, all these studies suffer from two important limitations: (1) retrospective design; and (2) definition of coronary patency as TIMI flow grade ≥2, not as just TIMI 3. Finally, measurements of these markers are often available too late, when irreversible myocardial damage has already developed. The rates of increase of serum myoglobin or troponin T during the first 60 min of thrombolytic therapy appear to be the only indices of reperfusion that may actually influence clinical management during the acute phase of MI. Until the newly developed 20 min rapid assay device for cardiac troponin T detection became available\[(42)\], these determinations were relatively expensive, lengthy procedures that were not routinely available in emergency laboratories.

**Other markers of reperfusion**

Probably via the inflammatory response to myocardial damage, MI causes a transient increase in the plasma levels of several acute phase reactants. Compared with persistent coronary occlusion, early coronary revascularization is associated with a blunted response of the acute phase reactants, including plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor, 24 h after initiation of thrombolytic therapy\[(48)\]. Similarly, during the first days of AMI, plasma levels of C-reactive protein are significantly reduced in patients achieving prompt coronary revascularization\[(49)\]. Although these markers are of pathophysiological interest, they provide only a late assessment of myocardial reperfusion.

It has been suggested that the lysis of coronary thrombi is associated with increased plasma levels of the specific fibrin split product known as D-dimer\[(49)\]. This is apparently not so, probably because thrombolytic drugs are capable of splitting not only the fibrin associated with coronary thrombi but also circulating soluble fibrin\[(50,51)\].

**Conclusion**

The early reduction of ST-segment elevation by >80% on the standard 12 lead ECG may correctly determine which patients have successful thrombolysis. These patients have, on average, a good outcome and do not need additional interventions. Conversely, lack of a significant (>20%) reduction in ST elevation on the standard 12 lead ECG may accurately identify the absence of reperfusion or the likelihood that revascularization was not successful. However, even in such patients, aggressive treatments are likely to be most cost-effective in high-risk subgroups, i.e. in patients with a large infarct (determined by the extent of ST elevation on the 12 lead ECG or by bedside echocardiography) or with poor left ventricular function (assessed by clinical signs of left ventricular failure or by echocardiography).

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