Thrombolysis and mechanical intervention following myocardial infarction

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In concept, mechanical interventions are attractive options for treating acute myocardial infarction with or without preceding thrombolysis: rapid reperfusion of the infarct-related artery can be achieved in the vast majority of cases, and the underlying coronary lesion is treated at the same time. Various strategies have been extensively investigated. When performed in specialized centres, direct percutaneous transluminal coronary angioplasty (PTCA) without prior thrombolysis appears to improve the outcome more than conventional thrombolysis. Whether this also holds true for the diverse range of hospitals remains unknown. Routine PTCA after thrombolysis did not show any benefit over thrombolysis alone. Rescue PTCA after failed thrombolysis is probably beneficial. Currently, only limited experience exists with other mechanical interventions, including intraaortic balloon pumping, thrombectomy with special new devices, or stent insertion, which need further investigation before they can be recommended for routine use in acute myocardial infarction.

Key Words: Acute myocardial infarction, PTCA, thrombolysis, infarct-related artery, reocclusion, perfusion.

Introduction

Mortality in acute myocardial infarction (AMI) is substantially reduced by early thrombolysis\textsuperscript{1,2}, mainly because of early reperfusion of the infarct-related artery (IRA)\textsuperscript{3}. However, at best only one half of the patients treated with thrombolytics in AMI experience optimal reperfusion with early, complete, and sustained infarct vessel patency\textsuperscript{4,5}. It seems plausible, therefore, that the outcome of AMI can be further improved by adding mechanical interventions — particularly percutaneous transluminal coronary angioplasty (PTCA) — to thrombolytic treatment or to choose PTCA as the primary treatment in all or selected patients. The theoretical advantage of adjunctive or primary PTCA in AMI is rapid and complete reperfusion of the IRA without significant residual stenosis in the vast majority of patients. On the other hand, PTCA carries the risk of complications on its own; reocclusion is common, especially in acute coronary syndromes\textsuperscript{6,7}; and PTCA requires rapid access to a catheterization laboratory 24 h a day. Strategies involve different approaches, including PTCA without preceding thrombolysis, PTCA after successful thrombolysis, and PTCA for failed thrombolysis.

Direct PTCA without preceding thrombolysis

Primary PTCA in AMI has been introduced to increase the reperfusion rate of infarct arteries, avoid the bleeding risk of thrombolysis, and reduce the incidence of reocclusion. Ideally, it not only recanalizes the thrombotic occlusion of the IRA, but also treats the underlying coronary stenosis. Based on these considerations, numerous reports on the uncontrolled experience of this strategy have been published during the 1980s\textsuperscript{8-11}. The initial success rate in terms of early infarct vessel patency was reportedly in the range of 80–90%, with reocclusion and death rates comparable to those observed after thrombolytic treatment of AMI.

Three major controlled trials of primary PTCA vs thrombolysis in AMI were published in 1993\textsuperscript{12-14}. One of these was extended to more patients later\textsuperscript{15}. In these studies, 804 patients with AMI were randomized to immediate PTCA vs thrombolysis with tissue plasminogen activator (t-PA) or streptokinase. The procedure was not performed in 4–10% of patients allocated to PTCA, mostly because of spontaneous recanalization of the IRA at the time of coronary angiography or unsuitable coronary anatomy. PTCA success rates were reported to be up to 99% in the Primary Angioplasty in Myocardial Infarction (PAMI) study with respect to Thrombolysis in Myocardial Infarction (TIMI) grade 3 perfusion of the IRA\textsuperscript{12}. In the PAMI and Dutch trials, the combined incidence of in-hospital death and
Table 1  Randomized trials of primary PTCA in AMI

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Control</th>
<th>Success (TIMI 3, %)</th>
<th>Reinfarction (%) PTCA/control</th>
<th>Deaths (%) PTCA/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAMI</td>
<td>395</td>
<td>t-PA</td>
<td>99</td>
<td>2.6/6.5</td>
<td>2.0/10.4</td>
</tr>
<tr>
<td>Dutch study</td>
<td>301</td>
<td>SK</td>
<td>97</td>
<td>1.3/10.1</td>
<td>2.0/7.4</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>108</td>
<td>t-PA</td>
<td>93</td>
<td>0.0/3.5</td>
<td>4.3/3.4</td>
</tr>
</tbody>
</table>

PTCA = percutaneous transluminal coronary angioplasty; AMI = acute myocardial infarction; TIMI 3 = Thrombolysis in Myocardial Infarction grade 3 perfusion; PAMI = Primary Angioplasty in Myocardial Infarction; t-PA = tissue plasminogen activator; SK = streptokinase.

Figure 1  The odds ratios of death within 6 weeks of acute myocardial infarction are given as calculated by Michels and Yusuf.161 The control groups received thrombolysis without intervention unless clinically indicated. Direct PTCA (percutaneous transluminal coronary angioplasty) is PTCA performed without preceding thrombolysis; immediate PTCA is PTCA directly after thrombolysis; early PTCA is PTCA 1-3 days after thrombolysis; and delayed PTCA was scheduled usually >3 days after thrombolysis. None of the strategies of routine PTCA after thrombolysis improved survival, whereas direct PTCA significantly reduced early mortality. Rescue PTCA (after failed thrombolysis) is probably beneficial, although the risk reduction is not significant because of the small number of patients studied. (OR = odds ratio; CI = confidence interval.)

reinfarction was significantly lower in the PTCA-allocated groups12,13 (Table 1). A recent meta-analysis, also including some smaller trials, calculated an odds ratio of 0.56 for the 6-week mortality and 0.53 for the combined incidence of death and non-fatal reinfarction after PTCA vs thrombolysis in AMI (Fig. 1).16 The benefit from PTCA was especially pronounced in patients classified as 'not low-risk', of whom 2-0% vs 10-4% died in the PTCA vs thrombolysis groups in the PAMI trial12 (Table 1).

Left ventricular function was similar in both treatment groups in the PAMI and Mayo Clinic studies12,13. In contrast, the Dutch trial reported greater myocardial salvage by PTCA, demonstrated by smaller infarct size (estimated from enzyme release), and better global and regional left ventricular function17. The observed differences were more pronounced in patients with anterior MI and those presenting within 2 h after symptom onset.

The overall bleeding risk of immediate PTCA was similar to that of thrombolysis; most bleeding after PTCA occurred at the vascular access site. The risk of intracranial bleeding was higher in the thrombolysis group in the PAMI trials, in which four patients died of intracranial bleeding after t-PA treatment.

The studies described here give evidence in favour of primary PTCA in AMI, as compared to conventional thrombolytic therapy. The results should, however, be interpreted with caution. All trials were performed in high-volume PTCA centres, and the
reported interventional success rates of up to 99% in TIMI grade 3 perfusion of the IRA\textsuperscript{[12]} certainly do not reflect everyday clinical experience. An inherent limitation of studies comparing interventional with conservative treatment is their open design. The fewer centres and/or investigators that contribute, the larger is this possible source of bias. Therefore, additional large-scale studies including more centres are required which better reflect the 'real life' treatment of AMI. In a German multicentre registry including >70,000 consecutive PTCA procedures, 4.8% were performed for AMI with an in-hospital mortality of 10.6%. The evidence presented as yet, therefore, does not justify the general recommendation to treat every patient with AMI by PTCA rather than thrombolysis. Furthermore, for logistical reasons, in most European countries direct PTCA is feasible for only a minority of patients with AMI.

**Primary PTCA in cardiogenic shock**

It has been suspected that thrombolysis might be less effective in patients with AMI complicated by cardiogenic shock\textsuperscript{[18,19]}. Angiographic studies of patients with cardiogenic shock treated by thrombolysis documented less than average reperfusion rates\textsuperscript{[20]}. A meta-analysis of randomized studies on fibrinolysis in AMI indicates, however, that thrombolysis is effective despite the very high absolute mortality of patients with this condition\textsuperscript{[21]}

Evidence from uncontrolled experience suggests that PTCA might considerably improve the prognosis in this high-risk subgroup. The evidence was based on retrospective comparison of patients with cardiogenic shock with successful vs unsuccessful attempts of PTCA\textsuperscript{[22-24]}. This type of comparison, however, is inherently biased, since the poor outcome of the unsuccessfully treated patients is part of the advocated treatment strategy on an intention-to-treat basis. A recent report from a multicentre registry reported less favourable effects of PTCA in cardiogenic shock. The prognosis for patients referred for cardiac catheterization turned out to be better than for those without catheterization, whether or not they had PTCA\textsuperscript{[25]}. It seems, therefore, that selection bias contributes significantly to the apparently good outcome of patients with cardiogenic shock in some observational studies of interventional treatment. The true impact of immediate PTCA in cardiogenic shock can only be estimated from randomized studies that are currently under way\textsuperscript{[19]}

**PTCA after successful thrombolysis**

In most cases, successful thrombolysis in AMI leaves the IRA with a significant residual stenosis that may give rise to reocclusion. Immediate or deferred PTCA has therefore been presumed to further improve myocardial perfusion and thereby preserve the myocardium better than thrombolysis alone. Based on these pathophysiological considerations, a number of controlled studies were performed using different PTCA strategies after thrombolytic treatment for AMI. The studies differed in the timing of the intervention after thrombolysis from immediately after the infusion to delayed intervention within 1-2 weeks\textsuperscript{[16]}. None of these approaches demonstrated improved survival; a non-significant trend to worse outcome in the aggressively treated groups was observed throughout. Furthermore, a benefit from PTCA after thrombolysis is not apparent if the combined incidence of death and reinfarction is considered.

One reason for the lack of benefit of adjunctive PTCA may be the relatively high reocclusion rate and early reinfarction, attributable to the mechanical trauma to the IRA. It is also possible that adjunctive PTCA after thrombolysis does not improve myocardial perfusion in the majority of patients with TIMI 3 patency of the IRA. On the other hand, the uniformly negative overall results of the studies on routine PTCA after thrombolysis do not exclude a benefit of this approach in specific subgroups. These subgroups, however, are not clearly defined.

**PTCA after failed thrombolysis (rescue PTCA)**

Whereas routine PTCA after thrombolysis is unnecessary or even harmful, PTCA to recanalize a persistently occluded IRA after failed thrombolysis may be beneficial, since early perfusion of the IRA is an independent predictor of in-hospital survival\textsuperscript{[26]}. In 224 patients from four angiographic studies in AMI\textsuperscript{[26]} with an occluded IRA 90 min after thrombolysis, the mortality was 8.5% in those without further interventions, 4.3% in those with successful mechanical recanalization, and 10.5% in those who had an unsuccessful attempt to recanalize the IRA. This suggests that successful rescue PTCA may be beneficial, but an unsuccessful attempt would increase the risk. Several non-randomized studies uniformly reported an exceedingly high mortality of 25-40% in patients with unsuccessful rescue PTCA\textsuperscript{[16,27-30]}. Thus, the potential harm from unsuccessful procedures might outweigh the benefit from myocardial reperfusion in the successful cases.

The appropriate use of rescue PTCA requires an accurate, non-invasive diagnosis of failed reperfusion; otherwise, most patients would have to undergo catheterization resulting in many unnecessary invasive procedures. However, neither the clinical symptoms nor the electrocardiogram reliably reflect the actual perfusion status of the IRA. Diagnostic accuracy might be improved by serial creatine kinase or myoglobin assays, but this would substantially delay the possible intervention. Even in view of an angiographically occluded IRA shortly after thrombolysis, one could not be certain about the indication for rescue PTCA, since it cannot be predicted whether the vessel will soon reperfuse...
spontaneously with less trauma to the arterial wall and possibly less risk of reocclusion than by mechanical intervention. Therefore, the decision in favour of rescue PTCA is primarily based on individual consideration of symptoms, electrocardiography, and immediate angiography in doubtful cases.

The average success rate was found to be 80% (range 71-92%)\(^{[31]}\) in a meta-analysis of 560 patients from 12 non-randomized PTCA studies. Reocclusion occurred in 24% of the patients treated with t-PA and in 14% of patients treated with urokinase or streptokinase.

Only one randomized study on rescue angioplasty of meaningful size has been reported. It included 151 patients with first anterior MI (symptoms <8h) and occluded left anterior descending coronary artery ≥90 min after initiation of thrombolysis\(^{[32]}\). The time to randomization was 4.5 ± 1.9 h and intervention was technically successful in 92% of the patients allocated to PTCA. Resting left ventricular ejection fraction (30 day) was similar, but left ventricular function during exercise was significantly better in the PTCA group. The combined end-point of death or severe heart failure occurred in 6% and 17%, respectively (\(P = 0.05\)) of the angioplasty vs conservatively treated groups. Therefore, rescue PTCA for failed thrombolysis is probably beneficial; however, because of the small number of patients randomized, the improvement in mortality was not statistically significant.

**Other coronary interventions**

There are preliminary reports on the application of methods other than PTCA to recanalize the IRA in AMI. Technically, most of the so-called new devices can be used in elective procedures. Directional coronary atherectomy (DCA) has been used in five cases of anterior MI with proximal occlusion of the left anterior descending coronary artery. All were successfully recanalized with only minimal residual stenosis\(^{[33]}\).

Like DCA, transluminal extraction coronary atherectomy is attractive in concept because the thrombus is removed from the IRA. This approach has been used in eight cases; all infract vessels could be successfully recanalized without evidence of distal embolization\(^{[34]}\). Another new device has been developed to dissolve coronary thrombus employing the Venturi effect created by high-pressure jet. This 7-French catheter can only be applied in saphenous vein grafts, where thrombi could be removed in seven patients with unstable angina\(^{[35]}\).

Coronary thrombectomy has also been attempted by catheter aspiration or by using the PTCA balloon like a Fogarty catheter to withdraw the clot into the guiding catheter\(^{[36]}\). While these manoeuvres might be successful in selected individual cases, they are at best experimental and not useful for most patients with AMI.

Stents have been considered to be contraindicated in AMI, since the combination of preexisting clot with the foreign body would cause subsequent thrombotic occlusion. However, several promising preliminary reports from France documented low reocclusion rates even without aggressive anticoagulant therapy\(^{[37-39]}\). Thus, in threatened acute closure of the IRA, stent placement may be justified.

**Mechanical circulatory support in cardiogenic shock**

Cardiogenic shock is associated with excessively high mortality rates—at least 50%—that are not substantially reduced by thrombolysis or PTCA\(^{[40]}\). Circulatory support has been recommended with intra-aortic balloon pumping (IABP), the only widely available type of support\(^{[19,20]}\). Haemodynamic improvement is usually achieved by IABP, but the survival rate has not demonstrably improved unless immediate revascularization is achieved. Despite the lack of a controlled trial, IABP has become part of the standard therapy in cardiogenic shock complicating AMI.

Recently it has been shown that IABP provides systemic circulatory support as well as significantly enhanced coronary flow after PTCA, thereby preventing reocclusion\(^{[40]}\). Based on this observation, a randomized trial of IABP vs conventional treatment after recanalization of the IRA by direct PTCA has been conducted. The reocclusion rate was 8% in the IABP-allocated patients as opposed to 21% in patients treated conservatively. The composite end-point of death, stroke, reinfarction, or emergency revascularization was observed in 13% vs 24% of patients\(^{[41]}\). The complication rates of IABP were surprisingly low (major bleeding, 2%; vascular surgery, 5%)..

IABP is widely available, but its haemodynamic efficacy is limited. More efficient cardiopulmonary support is achieved by transcutaneous insertion of cardiopulmonary bypass, which can bridge even complete circulatory arrest. In a registry of 258 patients with cardiogenic shock caused by a variety of underlying diseases treated with this type of support, the overall hospital survival rate was 34%. Of the subgroup of 118 patients immediately referred to surgery, 42% survived\(^{[42]}\). The prognosis was particularly poor for patients in whom flow was established after >20 min. Such rapid establishment of percutaneous cardiopulmonary bypass will be possible in only a few highly specialized centres. If the system can be successfully inserted, it allows for safe, immediate revascularization even of complex coronary disease\(^{[43]}\).

Recently, a very effective technique of left ventricular assistance has been introduced with the haemopump, applied in 11 patients with cardiogenic shock complicating AMI\(^{[44]}\). In this group, the haemopump effected immediate haemodynamic improvement with an average increase in cardiac index from 1.6 ± 0.4 to 2.4 ± 0.4 l.min\(^{-1}\).m\(^{-2}\). Despite this, only four patients survived. Vascular complications with this technique are common because of the very large lumen arterial access.
The limited experience with new techniques of cardiopulmonary support suggests that despite the high efficacy in terms of haemodynamic improvement, the results in terms of survival are still disappointing. Further studies are needed before these very expensive strategies can be recommended for routine use.

References


