Reviews

Reperfusion in Acute Myocardial Infarction: How is the Future Shaping up?

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Thrombotic occlusion of a coronary artery has been associated with acute myocardial infarction (AMI) as early as 1793 when an autopsy was performed on Sir James Hunter, a famous surgeon who died suddenly following a violent argument with hospital administrators in London[1]. The connotation of the term "acute coronary thrombosis" was eventually reaffirmed following the seminal study of DeWood et al[2]. Thrombolytic agents were discovered in the 1950s and, following long debates about their clinical benefits[3], they entered routine clinical practice in 1986[4].

It is now evident that although fresh thrombus represents the major pathological finding in acutely occluded coronary arteries, it is found in less than 70% of the cases[5,6]. This is in keeping with the current success rates of thrombolytic trials that, even with the use of aggressive protocols, result in restoration of normal coronary flow (TIMI 3) in only 60 to 70% of the cases[7]. It seems that a considerable proportion of AMI might be due to spontaneous dissection and/or severe intramural hemorrhage and extensive plaque rapture, in the context of pre-existing atheromatosis. We know now that although soft, noncritical lesions are more prone to rupture and consequent acute thrombotic occlusion[8], rapid stenosis progression is not uncommon and complex stenoses are more at risk than smooth lesions to evolve into coronary occlusions[9]. Resolution of any overlying thrombus by thrombolytic agents in this respect is unlikely to restore adequate antegrade flow in the coronary artery.

Furthermore, the incidence of intracranial hemorrhage following thrombolysis is estimated between 0.26 to 2.17%, depending on pre-existing risk factors[10]. Thus, certain patient groups such as the elderly (>65 years), women, hypertensive patients and diabetics are at an increased risk of intracranial hemorrhage when subjected to thrombolysis. It has been shown that over 95% of patients presenting with AMI are acceptable candidates for primary angioplasty (PTCA), whereas up to 1/3 of cases are considered to have contraindications to thrombolysis[11]. Several patients are therefore being denied the benefits of revascularization in this respect and the possibility of direct revascularization seems to be a reasonable alternative.

Primary PTCA compared to thrombolysis

Since the first reported cases of primary angioplasty in 1983[12], several thousands of patients have been enrolled in randomised trials comparing the interventional approach with thrombolysis. Primary angioplasty performed in experienced centers offers higher patency rates of the infarcted vessel (85-90% at 90 min-

utes), decreased cost and length of hospital stay, lower stroke and reinfarction rates and lower 30-day and 6-month mortality as compared to thrombolytic therapy[13-18]. In an early meta-analysis of 10 trials, primary angioplasty achieved a 35% decrease in mortality compared to thrombolytic therapy alone[19]. Its beneficial effect was also reaffirmed in a recent meta-analysis involving 23 trials and 7739 patients[20]. The higher the risk of the patient, the greater the potential of primary angioplasty compared with thrombolysis[21]. Mechanical recanalization avoids the interstitial edema, contraction band necrosis and microvascular haemorrhage seen with thrombolysis. It also achieves higher early patency of the occluded artery, decreased reocclusion rate and probably increased collateral flow to non-infarct-related myocardium, thus allowing better healing of the infarcted area and less ventricular dilatation[7]. By achieving complete reperfusion of the infarct-related artery, primary angioplasty results in greater ST-segment resolution and reduces the risk of left ventricular free wall rupture compared with thrombolysis[22,23].

However, with increasing use of primary PTCA, interventional cardiologists realize that no-reflow phenomenon occurs after success.

All these may well translate into an improved short-term outcome as well as long-term survival. WC Robert's admonition, therefore, "when I have an acute myocardial infarction take me to the hospital that has a cardiac catheterization laboratory and open cardiac surgical facilities" stated almost 20 years ago[24], seems to be absolutely justified in 2002, and if anything is to be argued, this is only the need for surgical support.

Surgical back-up and operators' experience

The issue of cardiac surgical back up is currently under investigation. Although the ACC/AHA guidelines recommend standby facilities[35], evidence is accumulating that surgical back up may not be necessary in hospitals, which meet certain requirements[36,37]. The Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) trial on thrombolytic-eligible patients with AMI showed improved clinical outcome and reduced hospital stay with primary PTCA at hospitals without on-site cardiac surgery compared with thrombolytic therapy[38].

Primary PTCA also requires skilled operators performing at least 75 procedures per year[39,40]. In busy centers absolute case volumes may not be as important but institutional experience, in general, influences complication rates and procedural outcomes[41].

Timing of primary PTCA

While thrombolysis is a relatively simple therapeutic procedure available even in primary care settings, PTCA requires the availability of institutions with cardiac catheterization facilities. Timely admission of the patient to such a unit is not always possible and the time to treatment with primary PTCA, as with thrombolytic therapy, is a critical determinant of mortality[25]. In the GUSTO IIb trial the 30-day mortality rate of patients who underwent balloon inflation within 60 minutes after study enrolment was 1.0%, but beyond 91 minutes after enrolment 6.4%[26]. However, a pooled analysis of primary angioplasty versus thrombolysis trials have shown that, irrespective of the time to presentation, patients allocated to primary angioplasty have a lower rate of major adverse events both at short and long term[27]. On the contrary, thrombolysis is very effective within the first "golden hour" post-MI, but much less so beyond the first 6 hours following artery occlusion[27].

Recent studies have documented the safety and feasibility of acute transfer of patients with acute myocardial infarction admitted to community hospitals without catheterization laboratory[28,29]. This strategy has been associated with a significant reduction in the incidence of reinfarction and the composite end-point of death, reinfarction or stroke at 30 days when compared to thrombolytic therapy at the community hospital[28-30]. Primary results from the Danish Trial in Acute Myocardial Infarction-2 (DANAMI-2) multicenter randomised study show that patients with AMI and high-risk ST elevation admitted to non-invasive hospitals and transferred to invasive hospitals in less than 3 hours following randomisation, had reduced rates of death, clinical reinfarction or stroke compared with patients who received thrombolysis at the non-invasive hospital[31]. In the recently published CAPTIM trial, AMI patients were randomised to PCI or prehospital thrombolysis within 6 hours following the acute event. There was a trend towards a lower incidence of combined end-point of death/reinfarction/stroke (6.2%) and mortality (3.8%) with PCI as compared to thrombolysis (8.2% and 4.8%, respectively) but the difference was not significant[32]. In this trial, PCI was performed approximately 60 min later than thrombolysis and there was a no-

tably high rate of crossover from the thrombolysis to PCI group.

It seems, therefore, that acute transfer of patients with acute myocardial infarction within a time window of three hours from admission to a community hospital is safe and associated with improved outcome. In a recent retrospective analysis of 21,912 myocardial infarctions from Sweden, early revascularization was associated with substantial reduction in one-year mortality (relative risk 0.47, CI: 0.37-0.60). In this analysis, 35% of patients were revascularized within a median time of 3h and 15 min, whereas the remainder were revascularized within a median time of 4.5 days[33]. The presence of an open artery 12-62 days following an acute event results in reduced apoptosis at the site of infarction and this observation has been proposed as an explanation of the open artery hypothesis[34].

Adjunctive pharmacotherapy

Aspirin and heparin should be given to all patients undergoing primary PTCA. Pre-hospital administration of aspirin and heparin results in higher initial patency of infarct-related artery in patients with AMI[42]. Thienopyridines, ticlopidine or clopidogrel that appear to have a favourable safety profile, are probably indicated in the setting of acute myocardial infarction regardless of the use of stents[43]. These agents are also superior to anticoagulation with fewer cardiac events and less bleeding complications[44].

Several randomised trials have reported on the impact of stent use in primary PTCA[45-50]. There has been a tendency towards lower mortality with stenting, although not confirmed by all studies, as well as a significant reduction in the incidence of the subsequent target vessel revascularization (almost threefold). A recent meta-analysis also confirmed that primary stenting is superior to balloon angioplasty in reducing target vessel revascularization within the next year following AMI, although reinfarction or mortality rates were not affected[51].

In the STENT-PAMI trial[48], there was a slightly lower rate of TIMI 3 flow with stenting, thus raising the possibility of distal embolization of thrombus protruding through the stent struts at the time of deployment. Direct stenting without predilation has been reported to result in reduced microvascular injury and improved ST-segment resolution[52]. With increasing use of primary PTCA, it became apparent that the no-reflow phenomenon occurs in more than 10% of cases after successful coronary reperfusion[53,54]. Development of no-reflow has been related to severity of myocardial damage, size of risk area and occlusion status of the infarct-related artery[55]. Data from 891 patients enrolled in GUSTO IIb and RAPPORT trials identified increasing age, increasing heart rate and presence of visible thrombus in coronary angiogram as independent predictors of TIMI flow <3 following primary angioplasty[56]. Distal embolization in patients treated with primary angioplasty may also be visible even in the coronary angiogram and indicate the role of additional pharmacological interventions and/or mechanical devices to prevent and/or treat distal embolization[57]. The outcome is poorer in patients with no reflow after primary angioplasty with increased incidence of cardiac death, recurrent AMI, malignant arrhythmia, and congestive heart failure[58].

More recently lesion morphology has been associated with no-reflow phenomenon and large vessels with lipid pool-like image are at high risk for this complication[59]. No-reflow phenomenon seems to be multifactorial and involves endothelial and myocardial cells, atherosclerotic debris and platelet plugs[55,56]. Strategies to prevent this phenomenon should be targeted to each component. The concomitant use of antiplatelet agents such as platelet glycoprotein IIb/IIIa receptor antagonists seems to reduce the incidence of this complication and several trials have addressed the issue[60-62,98]. Results have shown better TIMI flows and reduced major adverse cardiac events at 6 months with the use of these agents, although restenosis rates were unaffected. Improvement of peak flow velocity and regional wall motion in the infarct area have been demonstrated with the use of IIb/IIIa following primary stenting[63,64], and these findings translated into a lower cumulative incidence of death, reinfarction, or stroke at six months as compared with thrombolysis alone[65]. The ADMIRAL trial[61] showed that early initiation of abciximab before stenting resulted in improved TIMI flow immediately after the procedure and at 6 months. At 6 month follow-up death rates were not different among groups, but stents with IIb/IIIa inhibitors offered the lowest ischemic target-vessel revascularization rate. The combined primary end-point of death/reinfarction/urgent target vessel revascularization at 30 days was reached by 6% in the abciximab group and 14.6% in the placebo group ($p=0.02$). This benefit was also maintained at six months. Early abciximab administration and presence of diabetes

were associated with maximum benefit. The CADILLAC study[62] randomised 2082 patients with AMI to undergo PTCA alone, PTCA plus abciximab, stenting alone, or stenting plus abciximab. At six months, the primary end-point, a composite of death, reinfarction, stroke, and revascularization of the target vessel, had occurred in 20.0% of patients after PTCA, 16.5% after PTCA plus abciximab, 11.5% after stenting, and 10.2% after stenting plus abciximab (P<0.001). However, there were no significant differences among the groups in the rates of death, stroke, or reinfarction. The rate of angiographically established restenosis was 40.8 % after PTCA and 22.2% after stenting (P<0.001), and the respective rates of reocclusion of the infarcted-related artery were 11.3% and 5.7% (P=0.01), both independent of abciximab use. This study, however, had had several limitations, such as late abciximab initiation (after coronary angiography) and exclusion of high-risk patients.

We have recently performed a meta-analysis of 19 randomized placebo-controlled trials (involving almost 20,000 patients) of intravenous glycoprotein IIb/IIIa receptor antagonists in patients undergoing percutaneous coronary intervention[66]. Mortality was significantly reduced at 30 days (approximately 30%), and including longer follow-up with no significant between-study heterogeneity. The relative risk reduction was largely similar in trials on patients with or without AMI. Considering acute MI trials only, mortality was significantly reduced both at 30-day (risk ratio 0.69, and 95% CI 0.45-1.05) and 6-month follow-up (risk ratio 0.76, and 95% CI 0.55-1.05)[66].

Angioplasty devices and techniques

Several mechanical strategies have also been evaluated in an effort to prevent microembolization and enhance myocardial perfusion. They include extraction atherectomy[67], rheolytic atherectomy with the Angiojet device[68], ultrasound thrombolysis[69], thrombectomy with the X-sizer catheter[70], and filter protection with the Guardwire and the Filterwire[71,72]. However, the administration of antiplatelet agents or mechanical filters may not be enough to prevent distal embolization[72]. Even the achievement of TIMI 3 flow does not necessarily imply optimal myocardial perfusion[73,74]. Distal embolization with capillary plugging and microcirculatory injury and dysfunction may occur during acute myocardial infarction[75].

Finally, newer techniques such as induction of mild systemic hypothermia with endovascular cooling are also being tried in patients undergoing reperfusion therapy in an attempt to limit the infarct size[118].

Cost

Several analyses have found primary PTCA not to be more expensive than the conservative strategy using thrombolysis[76-78]. Actually primary angioplasty may reduce costs by offering lower re-admission rates and shorter hospital stay[79].

Specific clinical settings

Elderly

Mortality among older patients with acute myocardial infarction is higher than in patients of younger age[80,81]. The effectiveness of thrombolytic therapy in the elderly (>75 years) has been questioned[82,83]. Primary PTCA is more effective than thrombolysis in this patient group and accomplishes reperfusion with a lower risk of intracerebral hemorrhage when compared to thrombolytic therapy[13,14,80]. Elderly patients undergoing primary revascularization have a higher complication and mortality rate than their younger counterparts[84,85]. Nevertheless, in a recent randomised trial on patients with AMI who were older than 75 years, primary angioplasty within the first 2 hours of admission had a significant survival benefit compared to thrombolysis without increased procedural complications[86].

Diabetics

Diabetics also appear to have a considerably better outcome with intervention rather than thrombolysis[87]. Other situations in which thrombolysis is relatively less effective is congestive heart failure[88] and occlusion of saphenous bypass grafts[89].

Prior coronary surgery

Patients with prior coronary artery bypass surgery (CABG) represent an increasing proportion of patients with AMI. In this clinical setting, primary angioplasty is associated with higher adverse events, although this is mainly due to high-risk clinical profile of these patients and worse procedural results in vein

grafts[90,91]. In patients with prior CABG, late cardiac survival seems to be much worse compared with patients without prior CABG. In addition, primary PTCA on vein grafts achieves TIMI 3 flow less often compared with native vessels and is associated with higher in hospital mortality[92].

Cardiogenic shock

The leading cause of death in patients hospitalised for AMI is cardiogenic shock and mortality rates ranges between 60 to 90% without treatment. The impact of thrombolysis in this respect is doubtful and mortality still exceeds 65%[4]. Successful primary PTCA has been claimed to reduce mortality rates to 30%[88]. According to the SHOCK randomized trial[93], in patients with cardiogenic shock, emergency revascularization did not significantly reduce overall mortality at 30 days. This was also the case in the small, prematurely stopped SMASH trial[94]. However, after 6 months there was a significant survival benefit in the SHOCK patients undergoing revascularization[93]. Prospective registries also suggest that early revascularization should be strongly considered for patients with acute myocardial infarction complicated by cardiogenic shock[95].

Recent studies on primary angioplasty in AMI complicated by cardiogenic shock, have shown that abciximab confers a synergistic effect on stenting, resulting in higher TIMI flow rates and improved short and long term outcome[96,97].

The future: facilitated angioplasty

Although the majority of patients subjected to thrombolysis are found to have a significant residual stenosis[99], routine empirical use of coronary intervention following thrombolysis has not been found beneficial in early trials; actually there was a trend towards increased mortality following intervention in this setting[100-102]. Recent data, however, from contemporary trials in the era of stents and IIb/IIIa antagonists, suggest a probable benefit of rescue PTCA in several distinct scenarios and that the pivotal mid-1980s studies suggesting no benefit or harm for coronary intervention after fibrinolytic therapy may no longer be relevant[103-106]. This is particularly true for cases of failed thrombolysis. The RESCUE trial[103] investigating the impact of angioplasty in patients with anterior myocardial infarction and angiographically demonstrated coronary occlusion reported a reduction in the composite end point of death or congestive heart failure at 30 days post-PTCA. PTCA after failed fibrinolysis (TIMI 0 to 1 flow) appears to significantly reduce early severe heart failure (3.8% vs. 11.7%), improve survival over 1 year in patients with moderate to large myocardial infarction (92% vs. 87%), and possibly reduce early reinfarction (4.3% vs. 11.3%). Similar trends were reported in other trials[106-109].

More importantly, mechanical reperfusion in AMI has been found to result in better flow and outcome when performed on open compared with occluded arteries[42]. The combination of low dose thrombolysis with subsequent angioplasty has been addressed by the PACT trial[109]. In this study, AMI patients subjected to rescue PTCA within 1 hour following half-dose t-PA (50 mg bolus) did not display higher rates of stroke or bleeding complications as compared to those treated with PTCA without previous thrombolysis. Left ventricular function, however, was significantly better in patients achieving TIMI 3 flow by the time of angiography or when achieved by angioplasty. Long-term follow-up studies have also indicated that when reperfusion occurs before primary angioplasty, outcomes are better with improved procedural outcomes, smaller infarct size, better preservation of left ventricular function, and reduced mortality[111]. This finding has encouraged new strategies to establish reperfusion before primary angioplasty with platelet glycoprotein IIb/IIIa inhibitors and/or low-dose thrombolytic drugs. A combination of half dose thrombolysis with platelet glycoprotein IIb/IIIa inhibitors in the GUSTO V trial[112] demonstrated similar rates of intracranial hemorrhage and disabling stroke compared with thrombolysis alone. There is evidence, however, that this combination might reduce angiographically evident thrombus in AMI[113]. The SPEED (GUSTO-4 Pilot) trial[114] studied 323 patients who underwent angioplasty with planned initial angiography 63 min following thrombolysis or half dose thrombolysis combined with platelet glycoprotein IIb/IIIa inhibitors. Early angioplasty patients had fewer ischemic events and bleeding complications than did patients not undergoing early angioplasty. Patients receiving abciximab with reduced-dose reteplase showed an 86% incidence of TIMI grade 3 flow at approximately 90 min and a trend toward improved outcomes. The standard definition of TIMI flow grade 3 was used in this trial, however, instead of the "3 heart beat definition" for dye to traverse the artery that was adopted

in other interventional trials. Should the same criteria have been used by the SPEED investigators, an approximately 96% TIMI 3 rate would have been expected[115]. A strategy of combined reperfusion using full dose pre-hospital thrombolysis and immediate angioplasty with stent implantation was safe and achieved high and early patency rates in a non-selected AMI population[116]. Observations from TIMI 14 trial, demonstrated greater ST-segment resolution following combination of low dose thrombolysis, platelet glycoprotein IIb/IIIa antagonist and mechanical reperfusion, as compared to full-dose thrombolysis alone[113]. Thus, both rescue angioplasty (artery closed before the procedure) and adjunctive angioplasty (artery open before the procedure) are beneficial in the setting of AMI.

This approach of facilitated angioplasty in order to reduce the time delay inherent with mechanical reperfusion is promising and is being currently studied in randomized trials[117]. It is theoretically at least compatible with the "open vasculature" hypothesis, which argues for the achievement of early flow, full microvascular flow, full epicardial flow, and sustained flow. It remains to be seen whether the higher efficacy can be combined with lower intracranial haemorrhage rates than those encountered with ordinary thrombolysis. The results of ongoing trials testing the clinical efficacy and safety of facilitated angioplasty (such as the FINESSE and ADVANCE-MI) are eagerly awaited in this respect.

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