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EDITORIAL

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

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ABSTRACT

Current evidence from several clinical trials indicates that primary angioplasty in patients with acute myocardial infarction (AMI) appears superior reperfusion therapy to immediate thrombolysis, even when transfer to an angioplasty center is necessary. Thus, organization of ambulance systems and adequate angioplasty facilities appears to be the key issue in providing the most effective contemporary reperfusion therapy for AMI. Furthermore, on-site primary coronary angioplasty in high-risk AMI patients at hospitals with no cardiac surgery on-site is nowdays considered safe, effective, and faster than angioplasty after transfer to a surgical facility.

Randomized trials have demonstrated the superiority of primary angioplasty with stent implantation over balloon angioplasty alone in the treatment of AMI, including patients with diabetes. Stent use has been associated with significant decreases in length of stay, major adverse cardiovascular events, and in-hospital mortality. Finally, because of the risk of stent thrombosis, the issue of whether drug-eluting stents are safe or even more beneficial than bare-metal stents in patients with AMI, as in other non-AMI patient groups, remains uncertain, although preliminary data seem to favour the use of drug-eluting stents.

KEY WORDS: *acute myocardial infarction, reperfusion, thrombolyis, primary angioplasty, coronary stents, antithrombotic agents*

INTRODUCTION

Acute myocardial infarction (AMI) has been associated with thrombotic occlusion of a coronary artery as early as in 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 term "acute coronary thrombosis" was well established in medical literature and its connotation was reaffirmed following the seminal study of DeWood et al in 1980.[2] Thrombolytic agents were discovered in the 1950s and, following long debates about their clinical benefits,[3] they entered clinical routine in 1986.[4]

However, 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.[5-7] 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.[8] It seems that a considerable proportion of AMI might be due to spontaneous dissection and/or severe intramural

ABBREVIATIONS
AMI = acute myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty

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hemorrhage and extensive plaque rapture, in the context of preexisting atheromatosis. We know now that although soft, noncritical lesions are more prone to rapture and consequent acute thrombotic occlusion, rapid stenosis progression is not uncommon and complex stenoses are at risk more 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. Mechanical reperfusion, therefore, appears to be necessary in at least a proportion of patients with AMI and these patients cannot be identified in advance.

Furthermore, the incidence of intracranial hemorrhage following thrombolysis is estimated between 0.26 to 2.17% depending on preexisting 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 VS 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. It is now clear that primary angioplasty performed in experienced centers offers higher patency rates of the infarcted vessel (85-90% at 90 minutes), decreased cost and length of hospital stay, lower stroke and recurrent infarction 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 with thrombolytic therapy alone.[19] Mechanical recanalization avoids the interstitial edema, contraction band necrosis and microvascular hemorrhage seen with thrombolysis.[8] Early patency of the occluded artery is higher with decreased reocclusion rate and collateral flow to non-infarct-related myocardium is probably increased, thus allowing better healing of the infarcted area and less ventricular dilatation.[18-20] 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 >20 years ago,[20] seems to be absolutely justified nowadays and if anything is to be argued this is only the need for surgical support.

PREREQUISITIES FOR INTERVENTION

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.[21,22] 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 90 minutes after enrolment, 6.4%.[23] It is now accepted that, although either fibrinolysis or PTCA can be considered within the first 12 hours from the onset of symptoms, the time interval for the implementation of primary PTCA should not exceed 2 hours after the diagnosis of AMI.[24]

Primary PTCA also requires skilled operators performing at least 75 procedures per year.[25,26] In busy centers absolute case volumes may not be as important but institutional experience, in general, influences complication rates and procedural outcomes.[27,28] The issue of cardiac surgical back-up is currently under investigation. Although the ACC/AHA guidelines recommend standby facilities, evidence is accumulating that surgical coverage may not be necessary.[29-31]

ANGIOPLASTY DEVICES AND ADJUNCTIVE PHARMACOTHERAPY

Aspirin and heparin (unfractionated or low molecular weight) should be given to all patients undergoing primary PTCA. A thienopyridine, such as clopidogrel, which appears to have a favourable safety profile should also be used regardless of the use of stents.[32] These agents are also superior to antocoagulation with fewer cardiac events and less bleeding complications.[33]

Several randomised trials have reported on the impact of stent use in primary PTCA.[34-41] There has been a tendency towards lower mortality with stenting, although not confirmed by all studies, and a significant reduction in the incidence of the subsequent target vessel revascularization (almost threefold) with stenting. In one of the larger of the trials (PAMI-STENT)[37] there was also 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.[42] The concomitant use of antiplatelet agents such as IIb/IIIa receptor blockers seems to reduce the incidence of this complication and several trials have addressed this issue.[43-46,91] 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,[47,91] and these find-

ings did translate into a lower cumulative incidence of death, reinfarction, or stroke at 6 months as compared with thrombolysis alone.[43] The ADMIRAL trial[45] showed that 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 IIbIIIa inhibitors offered the lowest ischemic target revascularization rate. The CADILLAC study[46] randomized 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% 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 difference in the incidence of the primary end point was due entirely to differences in the rates of target-vessel revascularization (ranging from 15.7% after PTCA to 5.2% after stenting plus abciximab). 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. 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.[90]

Several mechanical strategies have also been evaluated in an effort to prevent microembolization and enhance myocardial perfusion. They include extraction atherectomy,[48] rheolytic atherectomy with the Angiojet device,[49] ultrasound thrombolysis,[50] thrombectomy with the X-sizer catheter,[51] and filter protection with the Guardwire and the Filterwire.[52,53]

However, the administration of antiplatelet agents or mechanical filters may not be enough to prevent distal embolization.[54] Even the achievement of TIMI 3 flow does not necessarily imply optimal myocardial perfusion.[55,56] Distal embolization with capillary plugging and microcirculatory injury and dysfunction may be caused by the AMI process.[56,57] Nevertheless, a recent meta-analysis of 21 randomized trials conducted with adjunctive mechanical devices to prevent distal embolization in 3721 patients with AMI, indicated that the use of adjunctive mechanical devices to prevent distal embolization is associated with better myocardial perfusion and less distal embolization, but without an apparent improvement in survival.[58]

COST

Several analyses have found primary PTCA not to be more expensive than the conservative strategy using thrombolysis.[59-61] Actually primary angioplasty may reduce costs by offering lower readmission rates and shorter hospital stay.[62]

SPECIFIC CLINICAL SETTINGS

Elderly patients, especially >75 years old, have an increased mortality after AMI and thrombolytic therapy may be of limited value in this setting.[63,64] For patients 65 to 75 years old, thrombolytic therapy has been associated with a survival benefit, whereas among patients aged 76 to 86 years, it has been actually associated with a survival disadvantage.[47] Primary PTCA appears to have a particular advantage over thrombolysis for the management of AMI in the elderly and this has been a consistent finding in the initial primary angioplasty trials. Nevertheless, elderly patients undergoing primary revascularization have a higher complication and mortality rate than their younger counterparts.[65,66]

Diabetics also appear to have a considerably better outcome with intervention rather than thrombolysis.[8,28] Other situations in which thrombolysis is relatively less effective is congestive heart failure[67] and occlusion of saphenous bypass grafts.[68] Primary PTCA may also be beneficial in these patient cohorts[69] although graft angioplasty is associated with relatively higher adverse event rates.[70]

The leading cause of death in patients hospitalized for AMI is cardiogenic shock and mortality rates ranges between 60 to 90% without treatment. The impact of thrombolysis in this respect is doubtful[4] and mortality still exceeds 65%. Successful primary PTCA has been reported to reduce mortality rates to 30%.[67] According to the SHOCK randomized trial,[69] 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.[71] However, after 6 months there was a significant survival benefit in the SHOCK patients undergoing revascularization.[69] Prospective registries also suggest that early revascularization should be strongly considered for patients with acute myocardial infarction complicated by cardiogenic shock.[72]

THE FUTURE: FACILITATED ANGIOPLASTY

Although the majority of patients subjected to thrombolysis are found to have a significant residual stenosis,[73] routine empirical use of PTCA following thrombolysis has not been found beneficial in early trials; actually there was a trend towards increased mortality following intervention in this setting.[74-77] 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 PTCA after fibrinolytic therapy may no longer be relevant.[78-80,93] This is particularly true for cases of failed thrombolysis. The RESCUE trial investigating the impact of angioplasty in patients with anterior AMI and angiographically demonstrated coronary occlusion reported a reduction in the composite end point of death or congestive heart failure at 30 days post-PTCA.[78] PTCA after failed fibrinolysis (TIMI 0 to 1 flow) appears to significantly reduce early severe heart

failure (3.8% vs 11.7%) and improve survival over 1 year in patients with moderate to large AMI (92% vs 87%), and possibly reduce early repeat AMI (4.3% vs 11.3%). Similar trends were reported in other trials.[81-83]

More importantly, mechanical reperfusion in AMI has been found to result in better flow and outcome when performed on open than occluded arteries. The combination of low dose thrombolysis with subsequent angioplasty has been addressed by the PACT trial.[84] In this study, AMI patients subjected to rescue PTCA within one 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 produced 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.[85] This has encouraged new strategies to establish reperfusion before primary angioplasty with platelet inhibitors and/or low-dose thrombolytic drugs. A combination of half dose thrombolysis with IIb/IIIa inhibitors in the GUSTO V trial[86] did not demonstrate increased rates of intracranial hemorrhage or disabling stroke as compared with thrombolysis alone. There is evidence, however, that this combination might reduce angiographically evident thrombus in AMI.[91] The SPEED trial[87] studied 323 patients who underwent angioplasty with planned initial angiography 63 min following thrombolysis or half dose reteplase combined with 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.[89] Should the same criteria have been used by the SPEED investigators, an approximately 96% TIMI 3 rate would have been expected.[87] A retrospective analysis of the TIMI 14 data, also demonstrated greater ST-segment resolution following combination of low dose thrombolysis, IIb/IIIa antagonist and mechanical reperfusion, as compared to full-dose thrombolysis alone.[92,93] 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. 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.[89] It remains to be seen whether the higher efficacy can be combined with lower intracranial hemorrhage rates than those seen with ordinary thrombolysis. Recently, the CAPITAL AMI study showed that in patients presenting with high-risk STEMI, tenecteplase plus immediate angioplasty reduced the risk of recurrent ischemic events compared with tenecteplase alone and was not associated with an increase in major bleeding complications.[94]

FINAL PERSPECTIVE

It is now abundantly clear that primary angioplasty in patients with AMI remains superior to immediate thrombolysis, even when transfer to an angioplasty center is necessary.[95] Organization of ambulance systems and adequate angioplasty facilities appear to be the key issues in providing the most effective reperfusion therapy for AMI. Furthermore, on-site primary angioplasty in high-risk AMI patients at hospitals with no cardiac surgery on-site is nowdays considered safe, effective, and faster than angioplasty after transfer to a surgical facility; on-site angioplasty and transfer groups have reported to have similar 30-day outcomes and more rapid reperfusion.[96]

Randomized trials have demonstrated the superiority of primary angioplasty with stent implantation over balloon angioplasty alone in the treatment of AMI.[97,98] Stent use has been associated with significant decreases in length of stay, major adverse cardiovascular events, and in-hospital mortality.[95] Diabetics with AMI also benefit from this strategy with stent implantation,[99] which significantly reduces restenosis and enhances survival free from target vessel revascularization, independent of IIb/IIIa use; however, survival remains reduced compared with survival in nondiabetic patients regardless of reperfusion modality. Finally, because of the risk of stent thrombosis, the issue of whether drug-eluting stents are safe or even more beneficial than bare-metal stents in patients with AMI, as in other non-AMI patient groups, remains uncertain. Preliminary studies of use of drug-eluting stents comparing their results with use of bare-metal stents, indicate lower AMI and death rates in mid-term follow-up with drug-eluting stents.[100] Further studies are needed to clarify this important issue.

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