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New Frontiers in The Reperfusion of Myocardial Infarction

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Acute myocardial infarction (AMI) is a major cause of morbidity and mortality (1). It is estimated that around 30% of patients die within the first hour of the onset of symptoms (2). In-hospital mortality rates approach 10%, and an additional 10% of the survivors will die within the first year after myocardial infarction.

Over the last two decades, a better understanding of the blood coagulation and platelet function, the introduction of effective pharmacological agents, increased use of coronary angiography, the development of advanced percutaneous techniques such as, percutaneous transluminal coronary angioplasty (PTCA), and coronary stenting have made a dramatic change in the acute management of myocardial infarction. Fortunately, there has been a steady decline in the mortality rates following myocardial infarction during the same period.

Almost a century ago, Herrick postulated that the triggering event of myocardial infarction was coronary thrombosis (3). Herrick's hypothesis was proven by angiographic studies demonstrating that total occlusion of the coronary artery by a thrombus was present in 87% of AMI patients evaluated within 4 hours of symptom onset (4). Recent studies have elucidated a cascade of events leading to coronary artery occlusion by a thrombus. There is a disruption of endothelial barrier after atherosclerotic plaque rupture with exposure of subendothelial matrix and activation of the cellular components of the plaque which results in platelet activation, thrombus formation and finally coronary occlusion (5-8). Pathology studies after myocardial infarction (MI) and sudden ischemic cardiac death, showed layers of platelet thrombi in different stages of organization at the site of coronary occlusion supporting this theory (7, 9).

Nearly 80 years later, a better understanding of Herrick's initial vision made emergent reperfusion therapy, either pharmacological or catheter based, the goal in the treatment of myocardial infarction. We will try to summarize new strategies to quickly achieve this cardinal goal in the clinical setting.

New Concepts in Pharmacotherapy

Advances in Thrombolytic Therapy

The usual cause of MI in humans is an occlusive thrombus in the coronary artery (3). Over the last decade, the effective use of thrombolytic therapy has started a new era in the treatment of this major cause of morbidity and mortality. The therapeutic benefits of aspirin and/or thrombolytic agents after myocardial infarction support the critical role of platelets and thrombus formation. Activating plasminogen by thrombolytic agents in patients with MI dissolves the fibrin elements of the thrombus and reestablishes the coronary patency (10). Thrombolytic therapy has greatly improved the prognosis of patients with AMI by rapid recanalization of the infarct related artery (11-13). Large scale studies revealed that the early administration of thrombolytic agents was associated with significant reduction in mortality (10-13).

Large, multi-center trials have confirmed 18 to 47% mortality reduction in AMI after treatment with thrombolytic agents streptokinase (SK) (11), recombinant tissue plasminogen activator (rtPA or activase) (12), p-anisoylated plasminogen streptokinase activator complex (APSAC or anistreplase) (13).

New thrombolytic agents are being investigated with studies comparing them to rtPA or SK. Reteplase (rPA), thrombolysis-in-cardiac-amyloidosis (TNK), lanoteplase (nPA) are

derivatives tPA molecule. Activase has a short half life requiring continuous intravenous infusion to achieve therapeutic levels. Alterations in the molecular structure of rtPA provided longer half lives allowing the new agents to be administered by single intravenous bolus injection. Furthermore, structural changes of TNK and nPA created an increased fibrin specificity and effectiveness on platelet rich thrombi.

GUSTO-3 (Global Use of Strategies to Open Coronary Arteries trial) compared the new agent rPA and the wild type rtPA which is produced by using recombinant DNA technology using *Escherichia Coli* (14). Similar 24 hour, in-hospital, and 30 day mortality were reported with comparable incidences of bleeding complications. TIMI-10 and InTIME trials showed promising results with the new agents TNK and nPA respectively (15, 16).

Prourokinase (also known as saruplase or scuPA), staphylokinase, vampire bat salivary plasminogen activator are other new thrombolytic agents which demonstrated promising results in the preliminary studies (17, 18). Prourokinase is a naturally occurring human protein which is the precursor to urokinase. PRIMI (Prourokinase in Myocardial Infarction) trial compared scuPA to SK in MI patients presenting within 6 hours of symptom onset (17). scuPA resulted in higher rates of patent infarct related artery and fewer bleeding complications.

Staphylokinase is a 136 amino-acid protein produced by *Staphylococcus Aureus*. It can activate plasminogen. A small clinical trial revealed similar infarct related artery patency rates to rtPA (18).

Evidence from such trials leaves no doubt that time to treatment is the most important parameter in myocardial reperfusion (10-13). Patients treated in the first hour have the highest mortality benefit (19,20). The development of these new agents has started a new concept of "bolus thrombolysis", permitting administration of the thrombolytic agent as a single bolus. The simplicity of dosing may provide more rapid treatment of AMI patients and potentially improve the survival. Importantly, bolus thrombolysis may make the promising strategy of pre-hospital treatment of AMI more feasible (21).

Advances in Antiplatelet Therapy

Aspirin provided substantial mortality benefit in patients with AMI. A multicenter, multinational study, the Second International Study of Infarct Survival (ISIS-2) randomized 17,187 patients with acute myocardial infarction to receive 162.5 mg of oral aspirin daily for one month, or placebo (11). At 35 days, there were statistically significant reductions in vascular mortality

(23%) and reinfarction (55%) in the group receiving aspirin (11). Since this trial, the use of aspirin has become a cornerstone of therapy for patients with AMI. The recommended dose is 325 mg per day and it is continued indefinitely.

Despite the indisputable benefit with aspirin after AMI many patients have recurrent ischemic events even on aspirin therapy (22). Furthermore, an initially successful response to thrombolytic therapy may be offset by reocclusion (23). This has stimulated the search for the ideal adjunctive agent in attempts to inhibit the coronary thrombus formation.

The development and availability of the GPIIb/IIIa inhibitors has initiated a new era in our approach to myocardial infarction. Several studies are assessing the safety and usefulness of these compounds in the setting of acute myocardial infarction.

The success of thrombolytic therapy stems from its ability to activate plasminogen, lyse the occlusive thrombus, and restore the blood flow in 70% of the infarct related arteries (24). However, about 30% of occluded infarct related arteries still cannot be reperfused even with the best thrombolytic therapy regimen. Additionally, in the initial trials assessing available thrombolytic therapy, the incidence of coronary occlusion from rethrombosis was approximately 20%, and the incidence of reinfarction was 10% (25). Most of these occlusions occurred in the first 24 hour. One plausible cause of resistance to plasminogen activators or thrombolytic therapy is the presence of platelet-rich thrombus. Platelets are the richest source of circulating plasminogen activator inhibitor (PAI-1), hence can readily inactivate exogenously given plasminogen activators (such as tPA or streptokinase). Patients who undergo coronary thrombolysis with either streptokinase (26) or t-PA (27) exhibit an increase in their urinary excretion of metabolites of thromboxane, consistent with the activation of platelets by these thrombolytic agents.

There is strong clinical and experimental evidence supporting the pivotal role of antiplatelet therapy in treatment of AMI. The therapeutic benefit of combined antithrombotic therapy was strongly demonstrated in the ISIS-2 study, where the combination resulted in a doubling in the reduction of mortality that was observed in patients treated with either aspirin or streptokinase alone (11).

In a chronic, canine model of coronary thrombosis, Fitzgerald et al. demonstrated that tPA 10 $\mu\text{g}/\text{kg}/\text{min}$ induced reperfusion in 55 ± 7 minutes, but complete reocclusion occurred in 9/10 animals. Reocclusion was pre-

vented by combining plasminogen activating effects of tPA with antiplatelet effects of a GP IIb/IIIa inhibitor (c7E3, a genetically engineered chimeric monoclonal antibody that can inhibit GP IIb/IIIa receptor permanently) (28). In another experimental model, c7E3 Fab antibody suppressed the expression of PAI-1 by cultured microvascular cells (29), therefore this antibody may have a beneficial effect on the fibrinolytic balance of t-PA/PAI-1 along with the well known anti-platelet effects. Therefore, the use of GPIIb/IIIa inhibitors along with thrombolytic therapy may potentially provide improved infarct vessel patency, reduced vessel closure, and reinfarction. Another animal study by Garabedian et al. studied the ability of a peptide inhibitor of GP IIb/IIIa, eptifibatide, to accelerate endogenous fibrinolysis in a canine model. They compared fibrinolytic effects of eptifibatide and tPA. With heparin and aspirin, eptifibatide restored coronary blood flow with equal frequency to tPA (30).

In addition to the experimental and animal data supporting the use of these receptors in AMI, in the clinical setting Gold et al. administered an irreversible inhibitor of GP IIb/IIIa receptor, c7E3 Fab to patients who had angiographic occlusion of infarct related artery after acute anterior myocardial infarction (31). GPIIb/IIIa blockade resulted in normal blood flow at the infarct related artery without any further intervention in 7 out of 13 patients.

Despite the evidence supporting the important role of antiplatelet therapy as an adjunct to fibrinolysis, the trials of GP IIb/IIIa inhibitors in the setting of AMI have lagged behind their use for unstable angina and/or after percutaneous coronary intervention. RAPPORT trial (ReoPro in Acute Myocardial Infarction Primary PTCA Organization and Randomized trial) randomly assigned 483 patients to a bolus and 12 hour infusion of abciximab versus placebo during primary angioplasty (32). Composite endpoints of death, myocardial infarction and urgent repeat revascularization were reduced in the abciximab arm at 7 days (8.3% vs 3.3%, $p=0.015$), however there was no difference between the groups at 6 months.

PARADIGM (Platelet Aggregation Receptor Antagonist Dose Investigation for Reperfusion Gain in Myocardial Infarction) trial evaluated the use of competitive, non-peptide inhibitor lamifiban in combination with thrombolysis after AMI (33). Patients with ST segment elevation presenting within 12 hour of symptom onset treated with either SK or tPA were enrolled in this Phase II study. A composite of angiographic, continuous electrocardiographic and clinical markers of reperfusion was the primary endpoint. ECG monitoring demonstrated significantly enhanced reperfusion in patients treated with lamifiban. Small number of patients (34 patients) underwent elec-

tive 90 minute cardiac catheterization, and no effect was seen on early TIMI 3 flow. Excess bleeding was noted in lamifiban treated patients (transfusions in 16.1 of lamifiban treated patients vs. 10.3% placebo treated patients).

TIMI-14 trial compared thrombolytic therapy with tPA, and three different combinations of reduced dose tPA plus a non-competitive GP IIb/IIIa receptor inhibitor, abciximab, in approximately 900 patients presenting with myocardial infarction. The primary endpoint of the study the rate of TIMI-3 flow at 60 and 90 minutes. Patients in the abciximab arm received only 50 mg of tPA compared to standard dose of 100 mg. At 60 minutes 43% of patients in the tPA-only arm achieved TIMI-3 flow compared to 77% in the tPA plus abciximab arm (34). Similar pattern was noted at 90 minutes.

ASSENT-II, HERO-II, SPEED, GUSTO 4, APPLAUD, SYMPHONY are some of the other large scale studies that will prospectively assess these novel agents in the setting of acute myocardial infarction (35).

New Concepts in Catheter Based Therapy

Recognition of the thrombotic occlusion caused a dramatic change in the management of patients with AMI. Emergent reperfusion therapy became the cardinal goal in the treatment of myocardial infarction. Timely given thrombolytic therapy has a life saving benefit in these patients, however only about 50% of patients with AMI are eligible for thrombolytic treatment (36).

Angiographic substudy of GUSTO trial demonstrated another limitation of the thrombolytic therapy. Wide differences exist in the patency of infarct related artery after administration of various thrombolytic regimens. Even the most aggressive thrombolytic regimen with front loaded tPA restored normal angiographic blood flow (TIMI grade 3 flow as defined in the Thrombolysis in Myocardial Infarction trial) in only 54% of patients (23).

Additionally, in the initial trials assessing available thrombolytic therapy, the incidence of coronary occlusion from rethrombosis was approximately 20%, and the incidence of reinfarction was 10% (25). Most of these occlusions occurred in the first 24 hour.

The shortcomings of thrombolytic treatment fueled a number of randomized trials comparing pharmacotherapy and catheter based therapy as an initial strategy for reperfusion. These trials differ in the designs with respect to the thrombolytic agent, dosing, dose and duration of heparin, the time window from symptom onset to the enrollment and finally the endpoints.

GUSTO 2B trial randomized 1138 patients within 12 hours of myocardial infarction to intravenous thrombolytic therapy versus direct angioplasty (37). The primary endpoints of the trial were death, non-fatal MI, and disabling stroke at 30 days. TIMI 3 flow rate was 73 to 88% in the angioplasty group. The angioplasty group did better at 30 days (composite endpoints of 9.6% vs 13.7%, $p=0.033$). The benefit was not long-lasting however, at 6 months there was no difference in the composite endpoints (14.1% vs 16.1). One of the reasons for the lack of the difference might be lesser success rates of TIMI 3 flow with PTCA than previously reported.

Several other trials have been conducted to investigate the outcomes of myocardial reperfusion achieved by emergency percutaneous transluminal coronary angioplasty (PTCA) vs thrombolytic therapy. In an effort to answer this important question, a recent meta-analysis of 10 randomized trials involving over 2600 patients compared 30 day mortality and stroke rates between the two strategies (38). Thirty day mortality was 4.4% for 1290 primary angioplasty patients versus 6.5% for 1316 thrombolytic patients (34% risk reduction). Lower stroke rate was reported with angioplasty (0.7% versus 2.0%; $p=0.007$).

We have to mention that while thrombolytic therapy can be applied in most of the hospitals, the majority of patients with AMI do not have access to facilities in which emergency PTCA can be performed timely and safely. Furthermore, the benefit with primary angioplasty was possible with the experienced operators of the enrolling centers. Therefore, American College of Cardiology (ACC)/American Heart Association (AHA) guidelines clearly outlined the class I indication for primary PTCA in U.S.A. : "As an alternative to thrombolytic therapy only if performed in a timely fashion by individuals skilled in the procedure and supported by experienced personnel in high volume centers." (39).

Given the change in the catheter based reperfusion adding stents and new adjunctive treatment such as GP IIb/IIIa inhibitors, it is likely that there will not be similar trials of "plain old balloon angioplasty" vs thrombolytic treatment in future.

In the interest of space, we will not get into the other indications of PTCA after MI, such as "rescue" PTCA after thrombolytic therapy or elective PTCA after MI. The Plasminogen-activator Angioplasty Compatibility Trial (PACT) trial compared two different strategies: rescue PTCA versus primary PTCA (40). The trial was designed to compare ventricular function outcome in patients ran-

domized to PTCA versus thrombolysis plus PTCA for AMI. Delay in time to successful reperfusion (TIMI 3) resulted in significant loss of myocardium. Thus, combining different strategies of reperfusion such as thrombolytic treatment and primary PTCA may decrease delay to TIMI 3 flow, hence improve the outcome.

Stenting in Acute Myocardial Infarction

Stenting was initially considered to be contraindicated after acute myocardial infarction with the fear stent thrombosis. However, recent progress in the prevention of this problem with antiplatelet agents made stenting a acceptable approach to improve the results of primary angioplasty. The recent PAMI-stent (Primary Angioplasty in MI) trial randomized 900 patients to stent (using heparin coated Palmaz-Schatz stent) versus PTCA. Preliminary results demonstrate a similar acute angiographic success between the two groups with no statistical outcome difference at one month with the exception of reduced ischemia driven target vessel revascularization (TVR) in the stent group (41). These findings are similar to the recently presented GRAMI trial (42). In this smaller study of 104 patients with AMI, 52 patients had primary PTCA without stenting and the other half underwent a GR II stent placement. The in-hospital major adverse clinical events were reduced in the stent arm (19.2% vs 3.8%). At one year follow-up, the TVR rate was lower in the stent arm without reaching statistical difference (9.6% vs. 13.4%). We need further studies with longer follow-up to assess the role of stenting in AMI.

Conclusion

Over the past two decades, several therapies with proven benefit have become available to improve the outcome of a patient with AMI. Science has provided new options in fibrinolytic therapy (anistreplase, TNK-tPA, and lanetopase), antithrombin therapy (different types of low molecular weight heparin and direct thrombin inhibitors), and antiplatelet therapy (GP IIb/IIIa inhibitors, clopiogrel). This remarkable progress in pharmacotherapy is accompanied by novel concepts in catheter based therapy of AMI. How we combine these strategies effectively in different clinical settings remains to be answered. One can come up with an enormous number of combinations using different regimens at different doses, coupling with different catheter based interventions. We hope future experience and efforts will teach us rational ways of making choices.

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