Fibrinolysis for Acute Myocardial Infarction

Current Status and New Horizons for Pharmacological Reperfusion, Part 2

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Ancillary therapy in association with fibrinolysis may be classified into 2 general categories. Additional therapies may be used to facilitate, enhance, and sustain coronary reperfusion, ie, conjunctive therapy, or to minimize the impact of the ischemic insult to the myocardium and/or consequences of reperfusion injury, ie, adjunctive therapy.

Ancillary Therapy

Conjunctive Therapy

An important paradox associated with the use of fibrinolytic therapy is its procoagulant potential. The effect of fibrinolytic agents on platelets is complex, poorly understood, and controversial.[1] Conflicting evidence exists concerning the capacity of fibrinolytic agents to activate as opposed to diminish platelet activation; this may relate, in part, to differences in protocol design and methodology for assessment of platelet function, the type of fibrinolytic agent used, and the time course over which the studies are conducted.[1-14] Regardless of this controversy, exposure of clot-bound thrombin, when unmasked, becomes an extraordinarily potent platelet agonist that mandates conjunctive antithrombin and antiplatelet therapy as an essential component of any fibrinolytic strategy.[5] Activated platelets provide an abundant source of factor Xa on their surface and, through extrusion from their alpha-granules, emit plasminogen activator inhibitor-1, α_2 antiplasmin, platelet factor IV, and a variety of vasoconstrictor substances such as thromboxane α_2 and serotonin.[1,6,7] The latter substances have been demonstrated to be biologically active in humans. They have also been suggested as the mechanism for no reflow after apparently successful primary angioplasty for thrombotic coronary occlusion and, together with the hematologic mediators, antagonize the prospects of successful fibrinolysis.[8] Conjunctive antithrombin therapy with unfractionated heparin is also associated with platelet activation. In summary, the vascular accident causing coronary thrombosis and the therapeutic strategy that incorporates fibrinolysis set the stage for a complex interplay of opposing forces with unpredictable results.

Antithrombin Therapy

Although unfractionated heparin has been used in most fibrinolytic regimens, especially those that possess high fibrin specificity, uncertainty persists regarding the optimal timing, route of administration, and dose to be used. Recently, the role of heparin has been critically examined in the large phase 3 Intravenous lanoteplase for Infarcting Myocardium Early (InTIME)-2 study, which compared lanoteplase to recombinant tissue plasminogen activator (rt-PA).[9] Because of concern that the heparin dosage had contributed to an excess of intracranial hemorrhage, down-titration of the heparin infusion was undertaken at an earlier point, ie, 3 hours after fibrinolysis, if the partial thromboplastin time (PTT) exceeded 70 seconds. This modification was associated with a reduction in intracranial hemorrhage rate from 0.71% to 0.52% in the 5000 patients randomized to rt-PA. This issue was subsequently examined among 1491 additional patients receiving lanoteplase in an extension to the study, ie, the InTIME-2b study, in which the heparin bolus was omitted and an infusion of 15 U $\cdot$ kg^{-1} $\cdot$ h^{-1} (maximum, 1000 U) heparin was used.[10] After this alteration, there was a commensurate reduction in the intracranial hemorrhage rate from 1.12% in the original 10 037 lanoteplase-treated patients in the parent study to 0.87% in the InTIME-2b study. The recent publication of the InTIME-2 study highlights excess anticoagulation in the lanoteplase-treated group as evidenced by higher activated PTT (aPPT) peak levels early after initiation of fibrinolytic therapy.[11] It is noteworthy that this persisted even after the protocol amendment recommending 3-hour aPPT assessment. These and other observations on the use of unfractionated heparin have led to the revised AHA/ACC guidelines that in turn have been incorporated into some new fibrinolytic clinical trials.[12] These guidelines (class IIa) for patients undergoing reperfusion therapy with rt-PA provide for a bolus of unfractionated heparin of 60 U/kg (maximum, 4000 U), followed by an infusion of 12 U $\cdot$ kg^{-1} $\cdot$ h^{-1} (maximum, 1000 U/h) targeting a PTT of 50 to 70 seconds during the initial 48 hours with provision for down-titration at 3 hours if the PTT is $>$70 seconds.

The role of unfractionated heparin in conjunction with streptokinase (SK) therapy remains controversial. No difference in survival or in 90-minute patency was noted when heparin was used subcutaneously as opposed to intravenously in the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) I study.[13,14] The recent success-

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ful introduction of low-molecular-weight heparin therapy in patients with acute non–ST-segment elevation coronary syndromes has prompted exploration of its use in conjunction with fibrinolysis, given its resistance to enhanced anti–factor Xa activity, ease of administration, and stability of anticoagulant effect, coupled with avoidance of the need for laboratory monitoring. In modest-sized studies of SK with dalteparin and rt-PA with enoxaparin (Heparin Aspirin Reperfusion Trial, HART 2), there have been suggestions of enhancement of early coronary reperfusion.[15] Whether these data, the potential for reduced reocclusion, and the overall safety profile will ultimately lead to adoption of this strategy in conjunction with fibrinolysis is unclear. This is and will be the subject of larger phase 3 investigations.

The promise of direct thrombin inhibitors in providing significant advantage over unfractionated heparin, used in conjunction with fibrinolytic therapy, has yet to be realized. Because of the enhanced reperfusion efficacy of Hirulog versus heparin in patients receiving SK in the phase 2 angiographic study and buttressed by a favorable interaction between hirudin and SK demonstrated retrospectively in the GUSTO IIb trial, an ongoing phase 3 study of bivalirudin versus unfractionated heparin in conjunction with SK for acute myocardial infarction is in progress.[16,17] Hirulog Early Reperfusion/Occlusion (HERO)-2, a large-scale phase 3 mortality study, has completed enrollment and will be reported at the European Society of Cardiology meeting in September 2001.

Antiplatelet Therapy

The pivotal role of antiplatelet therapy as an adjunct to fibrinolytics has emerged from the International Study of Infarct Survival (ISIS)-2 study in which, surprisingly, aspirin alone imparted a therapeutic benefit equivalent to that of SK.[18] Together, this combination was not only additive but superior to either treatment alone. Subsequently, pathophysiological studies have identified the platelet as a key component of the coronary thrombus and awakened new understanding of its major role.[1,19] This appreciation, coupled with greater understanding of the multiple roles of platelets in modulating both macrovascular and microvascular occlusion, may explain, at least in part, the failure of optimal reperfusion with conventional fibrinolytic therapy.[20,21] This realization underscores the need for antiplatelet agents with therapeutic efficacy that is superior to that of aspirin.

The discovery that the intravenous glycoprotein IIb/IIIa platelet inhibitor abciximab was associated with early coronary reperfusion rates comparable to those achieved by SK reinforced the utility of pursuing this conjunctive approach with fibrinolysis.[22] The role of abciximab in potentiating fibrinolysis is complex and may relate not only to its attenuation of platelet mediators of thrombosis but also to its effect on distal microembolization and platelet-leukocyte clumping.[23,24] A number of phase 2 studies have been conducted that used a combination of abciximab and various fibrinolytic agents, including SK, r-PA, and rt-PA.[22,25] Combination glycoprotein IIb/IIIa platelet inhibitor therapy with the non–fibrin-specific fibrinolytic SK has resulted in excess hemorrhagic complications and early termination of this strategy in 2 phase 2 studies incorporating either abciximab or integrelin.[22,26] Data support the combination of rt-PA and integrelin, and other studies are underway that use various fibrinolytic/glycoprotein IIb/IIIa combinations. Comparison of results between different pharmacological regimens from phase 2 studies completed to date is difficult. However, when abciximab is given in conjunction with half-dose rt-PA, impressive incremental TIMI 3 patency was evident in the TIMI 14 study, ie, 72% versus 43% for rt-PA at 60 minutes ($P=0.0009$) and 77% versus 62% at 90 minutes ($P=0.02$).[22] Additional support for the concept of combined fibrinolytic glycoprotein IIb/IIIa platelet inhibitor therapy has emerged from ST-segment resolution observations in the TIMI 14 trial; hence, even among patients who achieved TIMI 3 flow, those assigned combination therapy were significantly more likely to achieve complete ST resolution than those assigned rt-PA alone (69% versus 44%, $P=0.0002$).[27] It has been suggested from data derived from GUSTO I that to achieve a 1% increment in survivorship with fibrinolytic therapy, a 20% absolute increase in TIMI 3 flow should be achieved. This interesting but oversimplified assumption fails to take into account the potential implications of combination strategies on microvascular perfusion, the frequency of reocclusion, and complicating intracranial hemorrhage. Two large phase 3 studies, GUSTO IV AMI and ASsessment of the Safety and Efficacy of New Thrombolytic regimens (ASSENT 3), have recently been completed, will be reported at the European Society of Cardiology meeting in September 2001, and should provide useful additional data on these points.

TABLE 1. Adjunctive Therapy

Myocardial protective agents
β-Adrenergic blockers
Nitrates
ACE inhibitors
Magnesium
Glucose insulin-potassium
Adenosine and its analogs
Na/H exchange inhibition
Antiinflammatory agents
Complement inhibition, anti-C5 MAB
Anti-TNFα
Neutrophil adhesion inhibition, anti-CD11/CD18
Antioxidants/free radical scavengers
Matrix metalloproteinase inhibitors

TNF indicates tumor necrosis factor.

Adjunctive Therapy

A variety of adjunctive strategies have been used to reduce myocardial injury associated with reperfusion therapy.[28,29] Reducing ischemia by protecting the myocardium and favorably modulating the determinants of myocardial oxygen consumption is an important component of any reperfusion strategy. Recent attention has focused on minimizing the effects of reperfusion injury through antiinflammatory, antioxidant, and other novel therapies. A full discussion of these

TABLE 2. Clinical Use of Fibrinolytic Therapy*

Clinical indications
Ischemic symptoms or equivalent ≤12 h
ST elevation >1 mm in ≥2 contiguous leads
Bundle-branch block presumed to be new
Contraindications, absolute
Active bleeding or bleeding diathesis
Prior stroke or intracranial pathology
Aortic dissection
Contraindications, relative
Severe uncontrolled hypertension (>180/110 mm Hg)
Oral anticoagulants and INR>1.5
Major recent trauma/surgery
Pregnancy
Noncompressible recent vascular puncture(s)
Recent laser therapy of retina
Cardiogenic shock

INR indicates international normalized ratio.
*Adapted from Reference 12.

strategies is beyond the scope of this review, but a summary is provided in Table 1.

Clinical Indications, Benefits, and Risks

Table 2 lists the indications and contraindications for fibrinolytic therapy in patients with presumed acute myocardial infarction. Estimates from the Fibrinolytic Therapy Trialists (FTT) overview of ≈60 000 patients suggest that significant benefit is achieved within 12 hours of symptom onset, with ≈30 lives saved per 1000 patients treated within 0 to 6 hours and 20 lives saved per 1000 of those patients presenting between 7 and 12 hours.[30] Although the FTT overview suggests a decline in benefit of 1.6 lives per 1000 patients treated per 1-hour delay, it is confounded by the presence of different fibrinolytic agents applied to a broader cross section of patients than those with ST elevation alone. There is now ample evidence to support particular benefit when treatment is applied within the first 60 to 70 minutes of symptom onset.[31] Because the acuity of the myocardial infarction and the territory at risk also modulates benefit and because clinical assessment of symptom onset is often difficult, it is reasonable to relax this temporal window in applying therapy to individual patients who have continuing symptoms and ECG evidence of myocardial injury. Despite the wealth of evidence supporting the life-saving potential of fibrinolysis, underutilization of this therapy remains a key challenge in clinical practice that requires continuing education and emphasis.[32] Two recent developments have reignited interest in prehospital fibrinolysis: (1) the disappointing findings of the Rapid Early Action for Coronary Treatment (REACT) investigators, demonstrating that despite intense public education, time from symptom onset to request for medical assistance continued to be delayed, and (2) approval of 2 novel bolus fibrinolytics for general use, facilitating rapid and easy delivery.[33–36]

Recently, the safety of fibrinolysis administered as a bolus rather than infusion has been challenged. In particular, it was suggested after a meta-analysis of several different fibrinolytic agents that bolus fibrinolysis is associated with an excess risk of intracranial hemorrhage.[37] Careful review of this issue has been undertaken elsewhere, and several problems with this evaluation have been identified.[38] Suffice it to say that meta-analysis of the 2 bolus agents in general use, r-PA and the triple-substitution mutant tenecteplase (TNK), in >30 000 patients reveals no evidence of excess in intracranial hemorrhage versus front-loaded rt-PA.

The 30-day mortality of placebo patients with acute myocardial infarction in the FTT overview varied dramatically from 4.6% for those <55 years of age to 25.3% for those >75 years of age.[30] Although the absolute benefit was greatest for patients between 65 and 74 years of age and significant for younger patients, statistical significance was not achieved for the ≈6000 patients >75 years of age. Interestingly, the patients who were >75 years of age exhibited an early hazard within the first 24 hours (26 more deaths per 1000 patients treated) despite substantial subsequent benefit evident on days 2 through 35, resulting in a net benefit of 10 per 1000 patients treated. Recent analysis of the FTT data for the ≈3300 patients >75 years of age presenting within 12 hours with only ST elevation or bundle-branch block reveals a mortality risk reduction from 29.4% to 26.0% ($P=0.03$).[39] This early hazard is likely mediated by at least 3 factors: reperfusion injury, myocardial rupture with electrical mechanical dissociation, and hemorrhagic stroke, which rises precipitously in the elderly, especially when more fibrin-specific agents are used.[20,40,41] In addition to advanced age and the use of more fibrin-specific agents, other risk factors for intracranial hemorrhage include a history of cerebrovascular disease, female sex, black race, low body weight, and hypertension on admission.[42,43] The actual mechanism by which the cerebral vasculature develops increased susceptibility to proteolysis is unclear, but degenerative processes such as amyloid deposition may be operational.[43]

Recently, the use of fibrinolysis in patients >75 years of age has been questioned on the basis of a retrospective cohort study derived from Health Care Financing Administration (HCFA) data in the United States.[44] This study found a hazard ratio of 1.6 (95% CI, 1.2 to 2.13) for women and a nonsignificant increase of 1.12 (95% CI, 0.81 to 1.55) for men >75 years of age who had received fibrinolytic therapy. Within this population, 72.6% received rt-PA and 26.3% received SK. Surprisingly, there appeared to be little difference among the very elderly patients on the basis of which fibrinolytic agent they received, whereas clinical trial data clearly point to an increased hazard of intracranial hemorrhage with rt-PA in this population.[2] The excess mortality among elderly women raises several questions about the importance of dosing by weight, the established increase in risk of myocardial rupture in such individuals, and the appropriateness of the patient selection and fibrinolytic regimens used. Also of interest in this registry study was the fact that among those patients who did benefit, there was no evidence of this until 4 days after therapy had been admin-

TABLE 3. Comparison of Mechanical Intervention and Fibrinolysis

	Mechanical Intervention	Fibrinolysis
Advantages	Superior early patency	Widely available with broad access
	Reduced residual stenosis, recurrent ischemia, and reinfarction	Little dependence on operator experience
	Less intracranial hemorrhage	Can be given promptly and on site
	Lower early mortality	Simple to give in bolus format
	Superior in cardiogenic shock	
	Contraindications to fibrinolysis	
Disadvantages	Critical dependence on operator experience	Systemic bleeding
	Limited access	Intracranial hemorrhage
	Longer time to treatment	

istered. It is our view that these data are hypothesis generating and worthy of further study. Indeed, this particular segment of the population, which is growing and currently comprises approximately one third of patients presenting with acute ST-segment elevation myocardial infarction, has been deemed to be those patients accruing particular benefit from primary percutaneous coronary intervention.[45] A randomized clinical trial of this population incorporating an optimally dosed contemporary pharmacological strategy versus the best contemporary percutaneous intervention seems highly desirable. Until there is clear evidence to the contrary, however, the weight of clinical trial data supports the use of fibrinolytic therapy among appropriately selected elderly patients.

Recurrent thrombosis with transmural ischemia as evidenced by ST elevation occurring in the region of the original culprit is ideally managed with urgent angiography and mechanical intervention as appropriate. When such facilities are not available, repeat fibrinolysis has been shown to achieve good symptomatic benefit with concomitant ST-segment resolution in most instances.[46,47] Although some have argued for using the same dose of rt-PA as that used initially if the presumed coronary arterial reocclusion occurs early, ie, within 1 hour of completion of the initial infusion, the European Cooperative Study Group has shown that half-dose fibrinolytic may be effective. Early re-treatment with SK or anisoylated plasminogen SK activator complex within the first 4 to 5 days of initial administration may precede immunizing antibody formation, but thereafter the incidence of allergic reactions and potential compromise of efficacy suggest that a nonimmunogenic agent such as rt-PA, r-PA, or TNK is preferable.[48]

Alternatives to Current Fibrinolytic Therapy

One of the most animated debates in contemporary cardiovascular medicine relates to the relative merits of primary mechanical intervention as opposed to fibrinolytic therapy for the management of acute myocardial infarction. Marshalling the evidence to support the options is confounded by the relatively small number of randomized, direct head-to-head comparisons between the 2 options, the general applicability of trial-based interventional data to the larger clinical community, and the rapidly changing components of the 2 strategies used.[45,49,50] The relative merits of these 2 approaches are summarized in Table 3.

The recently updated ACC/AHA Guidelines for the Management of Acute Myocardial Infarction provide a class I recommendation for primary PTCA "as an alternative to thrombolytic therapy in patients with AMI and ST segment elevation or new, or presumed new, left bundle branch block who can undergo angioplasty of the infarct-related artery within 12 hours of onset of symptoms or beyond 12 hours if symptoms persist, if performed in a timely fashion (balloon inflation within 90±30 minutes of admission) and supported by experienced personnel in an appropriate laboratory environment."[10] The importance of timely performance of primary angioplasty has been clearly demonstrated in recent reports that show a clear relationship between the time from door to balloon inflation and mortality.[51,52] A primary mechanical approach is clearly indicated in patients presenting with cardiogenic shock (especially if <75 years of age) and in those with contraindications to fibrinolysis.[53]

One of the most important new developments in mechanical intervention is the utility of the intracoronary stent, which largely circumvents acute occlusion and may, in selected circumstances, be used directly without the need for angioplasty. This advance notwithstanding, the size of the culprit vessel may be a key factor limiting the deployment of stents, with a substantial number of initially eligible patients excluded from randomized trials because of unsatisfactory reference vessel size.[45]

The advent of glycoprotein IIb/IIIa inhibitors has had a substantial impact on the evolution of percutaneous coronary interventions. In particular, it has alleviated concerns about the no-reflow state and impaired distal coronary flow after stent deployment and substantially ameliorated problems with acute thrombosis, distal embolization, and recurrent ischemia/reinfarction.[54,55]

Traditionally, pharmacological and mechanical reperfusion for acute myocardial infarction has been judged an unsatisfactory combination resulting in excessive bleeding and reduced angioplasty success. Invasive procedures with the requirement for additional heparin and platelet inhibitor therapy administered on a platform of recent or concomitant full-dose fibrinolytic therapy have promoted excessive hemorrhage.[45] It has also been argued that the prothrombotic effects of fibrinolysis potentiate intracoronary clot formation in conjunction with mechanical intervention and that the

excess bleeding may extend to the ruptured plaque itself, thus potentiating formation of intramural hematoma. Recently, Ross and coworkers[55] have reexamined this issue in the Plasminogen-activator Angioplasty Compatibility Trial (PACT), which examined reduced dose fibrinolytic using a 50-mg bolus of rt-PA versus placebo, followed by immediate planned rescue angioplasty. Infarct patency at the time of initial angiography was doubled in those patients receiving rt-PA (33% TIMI 3 versus 15% for placebo) and resulted in better left ventricular function and a trend toward lower 1-year mortality. Angioplasty success was comparable in both treatment groups, as was the incidence of major hemorrhage, and further studies of this potentially complementary approach are warranted.

An interesting novel alternative approach to coronary fibrinolysis involves the use of ultrasound technology. This technique, using metal wire guides in an energy-emitting probe at the tip of a coronary catheter (attached proximally to an ultrasound transducer), generates and then implodes microbubbles.[56] Cavitation around the catheter tip during the negative phase of the ultrasound wave facilitates the generation of microbubbles, which implode during the positive phase of the ultrasound wave, thereby leading to fragmentation of thrombus. Although sparing the surrounding arterial wall from injury, an interesting potential salutary additional effect is endothelial-independent smooth muscle relaxation, possibly mediated by a reversible disruption of the filament interaction in the vascular contractile apparatus. Early clinical studies are promising and demonstrate equal efficacy on both recent and older thrombi and intermediate efficacy on reduction of associated coronary stenosis that in most instances has required additional balloon angioplasty.[57]

Future Developments

Important ongoing and future research will unquestionably enhance our ability to deliver fibrinolysis to patients with acute myocardial infarction in a more timely, safer, and more effective fashion. Optimum selection of patients through accurate and simple algorithms that will readily identify the risks of both the infarction and the proposed therapy will be made either quickly in the field or with minimal delay after rapid transit to the door; selection will probably be facilitated by prior digital transmission of key clinical predictors and ECG information.[58] Appropriate dosing of a fibrin-specific agent, probably in bolus form, with the dose apportioned according to weight and possibly age, sex, and race will be provided.[59–61] This will be accompanied by optimal antithrombin and antiplatelet conjunctive therapy, probably enhanced with adjunctive therapy to limit reperfusion injury. Noninvasive assessment through the use of clinical, ECG, and biochemical markers will establish the success of the initial pharmacological strategy to permit seamless triage to invasive study of patients who may benefit from timely mechanical revascularization.

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