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Coronary Thrombolysis With Tissue-Type Plasminogen Activator (t-PA): Emerging Strategies

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Fundamental observations and the conceptual framework underlying coronary thrombolysis have a history dating back to 1789. Recent enthusiasm for it is predicated on the recently established safety of cardiac catheterization in critically ill patients, the high incidence of coronary thrombosis underlying acute transmural myocardial infarction and demonstrable benefit conferred to the heart and the patient when thrombolysis is initiated early after the onset of ischemia. Clot-selective activators of the fibrinolytic system offer promise for safe induction of coronary thrombolysis without marked predisposition to bleeding. One such activator, tissue-type plasminogen activator (t-PA), has been synthesized by recombinant deoxyribonucleic acid (DNA) technology, amenable to large scale production of pharmaceutical agents and hence widespread availability.

Initial clinical trials conducted with t-PA have demonstrated opening rates of completely occluded, infarct-related coronary arteries of approximately 75% without marked depletion of fibrinogen. The focus of research in progress includes: 1) noninvasive delineation of recanalization and estimation of the extent of myocardium salvaged by initial recanalization, 2) development of alternative routes of administration of thrombolytic agents potentially exploitable by paramedical personnel and, perhaps, high risk patients themselves, and 3) definitive elucidation of the extent to which benefits conferred by thrombolysis can be enhanced with adjunctive pharmacologic interventions as well as early angioplasty or surgery.

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Coronary thrombolysis and its antecedents are hardly novel. The phenomenon of fibrinolysis was recognized in 1789 by Morgagni (1), streptokinase in 1933 by the laboratory of Tillett and Garnen (2) and tissue-type plasminogen activator (t-PA) in 1947 by Astrop and Permin (3) although it was not isolated until the late 1960s (4) or purified in quantities needed for studies in vivo and clinical research until 1981 by Rijken and Collen (5). Although Fletcher et al. (6) administered streptokinase to patients with acute myocardial infarction as early as 1958, enthusiasm for this mode treatment did not become intense until Rentrop et al. (7) demonstrated its dramatic recanalization of occluded coronary arteries in 1979.

A curious cardiovascular investigator must ask why acceptance of the potential utility of this mode of therapy was so delayed. The initial studies of Fletcher et al. (6) soon inspired large scale cooperative trials (8,9). Chazov and coworkers (10) in the Soviet Union documented angiographically that recanalization could be elicited by coronary thrombolysis. However, appreciation of the possible value of this intervention was slow to develop.

Times have changed. Aggressive evaluation of patients with acute myocardial infarction was demonstrated to be safe by students of coronary vasospasm. The advent of the Swan-Ganz catheter and research spawned by the myocardial infarction research units (MIRUs) and specialized centers of research in ischemic heart disease (SCORs) established the safety of vigorous physiologic and pharmacologic interventions in patients sustaining acute myocardial infarction. Advances in angiography, image processing and physiologic assessments made it feasible to characterize potentially therapeutic interventions safely and almost routinely in critically ill patients.

Goals of Thrombolysis

One other factor contributed to the recent enthusiasm for coronary thrombolysis. The hypothesis that the extent of myocardial injury would reflect the balance between myocardial oxygen supply and oxygen requirements gained cre-

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dence as a result of observations in numerous studies in experimental animals and patients (11). However, it became progressively clear that, in itself, reduction of myocardial oxygen requirements could attenuate only modestly the ravages of ischemic injury (12). Enthusiasm was therefore intensified for augmentation of nutritive myocardial perfusion, which is, after all, the factor most definitively responsible for maintenance of myocardial viability.

Results of numerous studies attest to the efficacy of coronary thrombolysis for recanalization. A substantial majority of patients with documented thrombotic coronary artery occlusions manifest recanalization within 60 to 90 minutes after treatment with an activator of the fibrinolytic system (13). However, the extent to which recanalization is beneficial remains to be established unequivocally. Efficacy of coronary thrombolysis cannot be judged simply in terms of recanalization. Restoration of nutritive flow, restitution of intermediary myocardial metabolism, salvage of jeopardized ischemic myocardium, maintenance of left ventricular function and prolongation of life are the end points on which enthusiasm for such therapy must be based (14).

Cautious investigators appreciate the fact that coronary thrombolysis cannot be viewed as a panacea. Most patients subjected to coronary thrombolysis exhibit high grade residual atherosclerotic disease in the infarct-related vessel and in other coronary arteries. The "no reflow" phenomenon is not merely an experimental artifact. It occurs in animals subjected to transitory ischemia followed by reperfusion and undoubtedly in patients as well (15). Thus, one cannot assume that recanalization implies commensurate nutritive reperfusion. As shown in studies, such as those with positron emission tomography, that use quantitative end points, the initial restoration of nutritive blood flow after ischemia followed by reperfusion may not be sustained. Furthermore, the extent to which regional myocardial metabolism can be restored by reperfusion is clearly inversely related to the duration of antecedent ischemia (16). Observations such as these underscore the importance of critical assessment of the efficacy of coronary thrombolysis on myocardium and the patient as well as on the recanalized vessel so readily visualized angiographically.

Attributes of Activators of the Fibrinolytic System

The fibrinolytic system and role of t-PA. The fibrinolytic system involves numerous constituents, some of which are summarized in Table 1. Its "business end" is attributable to plasmin, a proteolytic constituent generated from a zymogen, plasminogen, found in circulating blood. Under physiologic conditions, the presence of a clot within the vascular system elicits elaboration of an activator of plasminogen—tissue-type plasminogen activator (t-PA)—from endothelial cells. This moiety converts plasminogen to plasmin, a protein capable of degrading fibrin in clots and numerous other proteins. Under physiologic conditions, plasminogen, a circulating protein, binds to fibrin in intravascular thrombi as does t-PA. With fibrin present, the affinity of t-PA for plasminogen is high, the generation of plasmin is localized to the thrombus and clot lysis ensues without elaboration of plasmin into the circulation. However, when conversion of circulating plasminogen is induced iatrogenically by administration of an agent such as streptokinase or urokinase, concentrations of plasmin in the circulation increase massively, giving rise to what has been called a systemic lytic state predisposing to bleeding (17). High concentrations of circulating plasmin degrade fibrinogen, giving rise to fibrinogen degradation products—moieties with potent anticoagulant properties and antiplatelet actions. As a result, the patient is compromised by the risk of a bleeding diathesis.

Table 1. Components of the Fibrinolytic System

Plasminogen	A proenzymne of plasmin
Plasmin	The active enzyme that hydrolyzes fibrin (or fibrinogen)
Tissue and vascular activators of plasminogen	Enzymes in tissues that convert plasminogen to plasmin
Blood plasminogen activator	Plasminogen activator present in blood, probably identical to vascular plasminogen activator
Streptokinase	A streptococcal protein that complexes with plasminogen, thereby forming an activator in human plasma
Urokinase	A plasminogen activator isolated from urine which hydrolyzes plasminogen
Hageman factor; high molecular weight kininogen; prekallikrein	Plasma proteins involved in intrinsic activation of plasminogen
α_2-Antiplasmin	The fast-reacting plasmin inhibitor in human plasma

Under physiologic conditions, excess plasmin formed by t-PA and plasminogen bound to fibrin will be neutralized by circulating α_2-antiplasmin in a fashion analogous to the neutralization of hemoglobin by circulating heptaglobin. However, when circulating plasminogen is converted to plasmin after administration of streptokinase or urokinase, the α_2-antiplasmin system is overwhelmed. Consequently, free plasmin accumulates in the circulation, giving rise to nonspecific and potentially deleterious proteolysis.

Studies in experimental animals given t-PA. The utility of human tissue-type plasminogen activator for coronary thrombolysis was demonstrated initially in experimental animals in which coronary thrombosis was induced by percutaneous advancement of a copper coil into a coronary artery (18). Intravenous doses of human t-PA of the order of 0.1 mg/kg body weight elicited coronary thrombolysis demonstrable by angiography within 15 minutes. Coronary recanalization was accompanied by restoration of nutritive perfusion demonstrable by positron emission tomography,

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which also demonstrated restoration of intermediary metabolism of previously compromised myocardium. Of particular importance, concentrations of circulating fibrinogen were not diminished under these conditions as they are when coronary thrombolysis is induced with therapeutically equipotent doses of streptokinase. These initial observations demonstrated that clot lysis could be achieved by administration of t-PA systemically without induction of a systemic lytic state predisposing to bleeding.

Clinical studies with t-PA. Predicated on these results in experimental animals, analogous studies were implemented in patients with transmural myocardial infarction in progress and angiographically documented coronary thrombosis (19). Administration of comparable doses of human from the spent culture media of Bowes melanoma cells elicited recanalization of thrombosed coronary arteries in six of the initial seven treated patients without depleting circulating fibrinogen substantially and, hence, without inducing a systemic lytic state. Equipotent doses of streptokinase consistently reduce circulating fibrinogen by approximately 80% and give rise to massive elevations of fibrinogen degradation products with their consequent anticoagulant properties.

Encouraged by these observations we and others initiated a multicenter cooperative trial supported by the Genentech Corporation (20). Large doses of human t-PA were used. The t-PA employed was produced by recombinant DNA technology, a promising approach for production of large quantities of potentially pharmacologically useful agents (21). At doses of approximately 0.5 mg/kg, 75% of patients with angiographically documented coronary artery thrombi exhibited recanalization within 60 minutes after the onset of infusion of intravenously administered t-PA (20). Circulating fibrinogen declined only modestly, if at all, in patients treated in this fashion. Thus, results in the multicenter cooperative trial confirmed those obtained in our initial pilot study and supported the view that t-PA could elicit clot lysis safely without induction of a systemic lytic state. Confirmation was soon evident in the Thrombolysis in Myocardial Infarction (TIMI) trial supported by the National Heart, Lung, and Blood Institute (22) and in the European Cooperative study (23). In both of these studies, the incidence of recanalization was of the same general magnitude and the extent of depletion of circulating fibrinogen was comparable with that in our initial report and in the Genentech trial.

The Need to Avoid "Killing the Goose That Lays the Golden Egg"

Although t-PA and other clot-selective activators of the fibrinolytic system exhibit preferential affinity for plasminogen bound to fibrin compared with circulating plasminogen, it would be naive to think that any agent would be entirely devoid of potential toxicity (24). In fact, t-PA has some affinity for circulating plasminogen. As a result, flooding of the circulation with high concentrations of t-PA can elicit elaboration of plasmin in the circulating blood, consequent degradation of fibrinogen, generation of fibrinogen degradation products, consumption of α_2-antiplasmin and, ultimately, induction of a systemic lytic state (25). This potentially untoward set of events should not be surprising. No agent, even water, is devoid of toxicity when the dose is excessive. Simulation of the myriad reactions participating in fibrinolysis with the use of a physiologically based computer model predicts some consumption of fibrinogen and plasminogen under conditions in which circulating concentrations of t-PA are inordinately high or are elevated for extremely prolonged intervals. Agreement between predicted and observed alterations of concentrations of constituents of the fibrinolytic system is close (26). Such simulations provide potentially useful boundaries for anticipating the deleterious effects of excessively prolonged or excessively high doses of t-PA and provide criteria for establishing dose regimens for treatment of specific entities ranging from deep venous thrombosis to cerebrovascular disease under conditions in which a systemic lytic state must be avoided.

Prevention of Reocclusion of Recanalized Coronary Arteries

The biologic half-life of t-PA is of considerable importance with respect to prophylactic as well as therapeutic applications of the agent. In circulating blood, t-PA disappears with a half-life of approximately 5 to 8 minutes (17). The biologic half-life of t-PA bound to fibrin is more prolonged. Thus, once t-PA has been administered and bound to fibrin in the nidus of intravascular thrombi, activation of plasminogen locally can proceed even when circulating concentrations of t-PA decline to physiologic levels. By the same token, the potentially deleterious systemic effects of elevation of concentrations of t-PA in the circulation can be obviated promptly by cessation of administration of the agent in view of its short half-life in circulating blood. These considerations are particularly pertinent to prevention of reocclusion of initially recanalized vessels. It has been shown in studies in experimental animals (27) that blood concentrations of t-PA approximately 10% as high as those required to lyse established coronary thrombi are sufficient to preclude reocclusion of coronary arteries in which a thrombogenic copper coil has been inserted. Infusions of t-PA in low quantities, sufficient to achieve such concentrations in circulating plasma, appear to be devoid of deleterious consequences and do not induce a systemic lytic state. These observations are compatible with results in vitro data demonstrating that lysis of established thrombi requires concentrations of t-PA in plasma 10- to 100-fold or more higher than concentrations required to lyse thrombi formed in the presence of t-PA.

Methodologic Considerations

Unfortunately, much confusion surrounds evaluations of the relative toxic to therapeutic ratios of different activators of the fibrinolytic system. Assessment of the effects of activators on constituents such as α_2-antiplasmin, plasminogen, fibrinogen and fibrinogen degradation products requires acquisition of samples under conditions in which fibrinogenolysis is precluded in vitro and potential effects of activator in the sample are attenuated. Most investigators supplement samples with aprotinin for this purpose. However, this inhibitor of proteolysis does not preclude conversion of plasminogen to plasmin by activator in the sample, particularly when samples are subjected to repetitive freezing and thawing. One approach that appears to be more effective is inclusion of PPACK, a serine protease inhibitor, in samples acquired for assessment of the extent of fibrinogenolysis in vivo (26). This inhibitor can be added in excess. It binds to an activator such as t-PA present in high concentration in the sample after administration in vivo. Residual, free PPACK in the sample undergoes spontaneous degradation under defined conditions such that assays of constituents of the fibrinolytic system can be performed without artifact even though functional activity of t-PA in the sample has been precluded. With the use of PPACK, we demonstrated that a considerable fraction of the apparent fibrinogenolysis induced by high doses of t-PA such as those employed in the TIMI trial is attributable to artifactual formation of plasmin in vitro and consequent fibrinogenolysis in the sample rather than in the patient (26).

Augmentation of Benefit to the Patient

Avoiding delay in the onset of therapy. In a recent editorial, Rentrop (13) presented a somewhat bleak picture regarding restoration of ventricular function by coronary thrombolysis. However, as he noted, the most likely factor responsible for failure of thrombolysis to restore pump function is the relatively protracted interval of ischemia before reperfusion even in rigorously performed studies. In experimental animals, the extent of myocardial salvage is inversely proportional to the duration of the ischemic interval before recanalization (16). Thus, we should not be surprised by a paucity of beneficial effects on the heart when reperfusion is delayed, as it is so often in patients who present relatively late after the onset of symptoms to the medical surveillance system.

Adjunctive pharmacologic measures. In addition to public health educational efforts required to reduce "delay time" such that patients present more rapidly after the onset of ischemia, adjunctive pharmacologic measures such as administration of calcium channel blocking agents may prolong the period during which jeopardized myocardium may remain salvageable (28). Thus, in dogs given diltiazem in doses of 15 μg/kg per min beginning immediately before reperfusion for 24 hours after an ischemic insult, myocardial salvage induced by thrombolysis is augmented by approximately 50%. Use of this intervention is based on the premise that augmented inward calcium flux as a consequence of impaired membrane function is a mediator of irreversible injury, perhaps because of its capacity to activate potentially destructive enzyme systems such as phospholipases. An additional rationale relates to the potential role of calcium in catalyzing formation of oxygen free radicals through the xanthine oxidase system and the potential amelioration of generation of such toxic products by calcium antagonists.

Intramuscular t-PA. An alternative emerging strategy addresses the potential for very early administration of thrombolytic agents. In recent studies we have demonstrated that absorption of intramuscularly administered t-PA is infinitesimal in the absence of agents facilitating its ingress into the circulating blood. However, when injectates are supplemented with hydroxylamine, therapeutic plasma levels of t-PA can be achieved with administration of overall intramuscular doses comparable with those given intravenously in conventional trials (29). Peak blood levels occur within 5 minutes after administration of the agent in this fashion, and potentially therapeutic levels are sustained for as long as 120 to 150 minutes. Although the approach must be viewed as quite preliminary because of unanswered questions relating to possible local injury of skeletal muscle, antigenicity of t-PA given by this route and potentially unexpected complications of administration of the agent under these circumstances, it is promising because of the potential it provides for administration of t-PA by paramedical personnel or by patients at risk and under adequate medical surveillance and guidance at the time of onset of symptoms.

Noninvasive Detection of Recanalization

Major issues confronting investigators and clinicians treating patients with presumed coronary thrombosis include these questions: 1) has recanalization occurred within a definable interval after the onset of ischemia, and 2) has such recanalization influenced a sufficiently large region at risk to justify aggressive diagnostic and therapeutic interventions to sustain the viability of tissue that may have been salvaged? The standard for answering the first question is coronary angiography. From a practical point of view, however, it is simply not feasible to subject all patients with suspected myocardial infarction and all patients who have been treated with activators of the fibrinolytic system to abort unstable angina, incipient infarction or evolving myocardial necrosis to angiography within the time frame needed to determine whether recanalization has occurred. Accordingly, efforts have been made to identify markers of myocardial injury that behave in a sufficiently disparate fashion when reperfusion is induced such that recanalization can be

inferred accurately from results of assays of blood samples in vitro.

Assays of subforms (isoforms) of creatine kinase MM isoenzyme: One such marker with particular promise is the derived, posttranslational product of the tissue form of the MM isoenzyme of creatine kinase (CK) liberated from myocardium undergoing injury. It has been demonstrated that the tissue form of CK MM (MM_A) undergoes posttranslational modification, or conversion, mediated by carboxypeptidase in plasma to yield MM_B and MM_C sequentially as a result of proteolytic cleavage of the carboxy terminus of the tissue isoenzyme. Kinetics of conversion are consistent, thereby providing a "chronometer" that can be utilized to discern the time of onset of release of the tissue form from myocardium and hence the time of onset of irreversible injury (30). When isoenzymes are liberated from injured myocardium as a result of reperfusion, the rate of rise of the tissue form in plasma is 10-fold or more greater than the rate of rise of the tissue form in plasma when enzyme is liberated spontaneously as a result of typically evolving acute myocardial infarction. Under such circumstances, concomitant conversion of MM_A to MM_B and MM_C blunts the relative rate of rise of MM_A. Accordingly, assay of two blood samples within a 30 minute interval for determination of the ratio of MM_A to MM_C may provide a reliable criterion of recanalization at a low cost and with potentially widespread availability (31).

Assessment of extent of salvaged myocardium. Determination of the extent of myocardium at least temporarily salvaged by reperfusion is an equally vexing and demanding task. In the research environment, assessment of the distribution of impaired perfusion with techniques such as positron emission tomography after intravenous administration of radiolabeled water, assessment of the distribution of impaired regional myocardial metabolism with positron tomography after intravenous administration of carbon-11–labeled palmitate and delineation of regional augmentation of glycolytic flux relative to blunted accumulation and oxidation of labeled fatty acid are promising approaches (32). However, such assessments cannot be applied universally for routine clinical evaluations. Delineation of the extent of necrosis incurred with respect to the region at risk will probably be made clinically with conventional techniques after appropriate calibration of results with quantitative research methods such as positron emission tomography or nuclear magnetic resonance spectroscopy.

Concluding Comments

Coronary thrombolysis is a promising approach to treatment. The advent of clot-selective activators of the fibrinolytic system offers promise of safe, widely applicable and rapid administration of thrombolytic agents in patients with suspected acute myocardial infarction under conditions in which appreciable salvage of myocardium can be anticipated. Recanalization alone is not an adequate end point of efficacy (33). Benefits to the heart and the patient must be demonstrable. Results of recently completed large scale clinical trials suggest strongly that coronary thrombolysis can reduce morbidity and mortality associated with acute ischemic insults and, perhaps of most importance, that coronary thrombolysis can "buy time" during which jeopardized ischemic myocardium can be maintained in a viable state while definitive diagnostic and therapeutic interventions are implemented. Noninvasive detection of recanalization appears achievable, and improved understanding of the mechanisms involved in activation of the fibrinolytic system with clot-selective as opposed to first generation thrombolytic agents offers promise for improving the efficacy and safety of thrombolytic therapy. Adjunctive approaches to reduce the rate of evolution and the ultimate extent of myocardial injury while reperfusion is being implemented appear particularly promising.

Although coronary thrombolysis is not a panacea, it appears to offer a potentially valuable first step for preserving viability of myocardium and broadening the interval during which invasive diagnostic procedures and aggressive therapeutic measures can be employed to definitely restore and maintain nutritive myocardial blood flow and myocardial metabolic and functional integrity.

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