A blood fluidity is a dynamic balance between thrombosis, its inhibition, and thrombolysis. In this vital balance, the process of clot formation and lysis produces new protein species. Activation peptides are formed when zymogens become active enzymes or when fibrinogen clots and enzyme inhibitor complexes develop as enzyme activity declines. Quantitative immunologic protein assays demonstrate nanomolar levels of activation peptides and enzyme inhibitor complexes in the plasma of normal people, indicating the dynamic nature and constant activity of these systems. Fibrinopeptide A, coagulant-inactive fragment of prothrombin, fibrinolytic fragment of the β-chain of fibrinogen, and thrombin-antithrombin complexes are examples. Therefore, the mechanism of balanced thrombus formation and dissolution appears to be the physiological means of maintaining fluid blood while having a ready system for rapid thrombosis when necessary.

Clot formation occurs when the equilibrium between thrombosis and fibrinolysis tips to favor thrombus formation. Equilibrium can be reestablished by administration of anticoagulants, leading to a reduction of thrombin production, or by administration of streptokinase or tissue-type plasminogen activator (t-PA), leading to enhanced plasmin generation. Fibrinolytic therapy not only alters the thrombin/plasmin balance in the circulation or on the clot surface but also enhances degradation of the pathological thrombus, reestablishing vascular patency.

In the past decade, we have seen an expanding role for therapeutic fibrinolysis in venous disease and arterial occlusive disease.

There are three limitations of therapeutic fibrinolysis as applied in acute arterial thrombosis. The first is failure to achieve initial clot lysis. Ninety minutes after infusion of streptokinase or t-PA, 20% of coronary arteries remain occluded. The second limitation is clinical hemorrhage. In the Urokinase Pulmonary Embolism Trial, 45% of those complications occurred at vascular puncture sites; the frequency has decreased as the number of invasive studies has decreased. Intracranial hemorrhage occurred more frequently with fibrin-selective t-PA than with streptokinase. Reduction of the dose of t-PA infused from 150 to 100 mg has been associated with diminished intracranial hemorrhage in patients receiving this agent. The third limitation of fibrinolytic therapy is recurrent thrombosis of a vessel in which fibrinolytic therapy achieved initial recanalization. Reocclusion occurs in 10–20% of coronary vessels patent after thrombolysis.

In this issue of Circulation, Haskel et al report a new approach to this problem by using lipoprotein-associated coagulation inhibitor (LACI), which inhibits tissue factor VIIa activation of the extrinsic system. The authors describe a canine model of two different mechanisms of arterial thrombosis. In one femoral artery, thrombosis was induced by application of electric current through a transluminal electrode; the current also induced vascular injury extending into the subendothelium. An occlusive thrombus formed in the contralateral artery subsequent to insertion of a coil of copper wire; the underlying subendothelium was intact and microscopically normal. Thirty minutes after complete thrombotic occlusion, recombinant human t-PA was infused over 60 minutes. Immediately after completion of t-PA infusion and thrombolysis, LACI or saline was administered for 120 minutes. The incidence of reocclusion after successful thrombolysis was measured 120 minutes after discontinuation of t-PA. LACI had no effect on the incidence of rethrombosis on the side in which copper wire clots were lysed. However, LACI did reduce the rate of rethrombosis in vessels damaged by electric current from seven of seven vessels in saline controls to zero of five vessels in LACI-treated animals. In addition, the frequency of cyclic flow variations decreased from 13.7 ± 5.5 per hour in controls to 0.4 ± 0.4 per hour in LACI-treated animals.

The causes of reocclusion of a vessel initially patent after thrombolytic therapy must be multiple. The data of Haskel et al suggest that the type of vessel damage will influence the pathogenesis of vascular reocclusion and the interventions successful in its prevention. The underlying conditions tipping balanced thrombosis/fibrinolysis toward thrombosis

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may persist. Local levels of plasminogen activator may be decreased; this protein is synthesized in the endothelial cell, which is one of the cells injured by atheroma. Fibrin-bound thrombin is released from the clot; it can clot additional fibrinogen and initiate or potentiate platelet aggregation as well. Native factor V is converted to factor Va by plasmin and could potentiate thrombus formation. Tissue factor in contact with circulating blood could activate the extrinsic coagulation mechanism with clot formation. A severely stenotic vessel with diminished flow velocity could permit accumulation of procoagulants and potentiate rethrombosis. High local shears at the site of stenosis or downstream turbulent flow may activate platelets.

Post-thrombolysis anticoagulation may prevent rethrombosis by reestablishing balanced thrombosis/fibrinolysis at diminished activities of both sides of the equation. Heparin, low-dose warfarin, and aspirin have been used clinically to reduce recurrent thrombosis after successful fibrinolytic therapy. In the International Study of Infarct Survival, addition of aspirin to streptokinase reduced infarct mortality to 8% compared with 10.2% in the patients who received streptokinase alone and 13.4% in those receiving no fibrinolytic therapy. A lower incidence of coronary rethrombosis would explain these data. Other platelet-inhibiting agents may also be useful. In a canine model, administration of antibody to platelet glycoprotein IIb-IIIa stabilized blood flow in coronary arteries recanalized by t-PA. In a canine study, infusion of hirudin reduced thrombin activity more than heparin administration, demonstrating good potential as an agent to prevent rethrombosis through thrombin inhibition.

The data of Haskel et al. may be pertinent to the question of which approach to preventing rethrombosis is likely to be useful. Of the two mechanisms of thrombosis in this model, the electrically damaged vessel may be hemostatically similar to that of a vessel damaged by atherosclerosis. Decimated endothelium and internal elastic lamina are seen in both the electrically damaged and atherosclerotic vessels but not with the copper coil model. Tissue factor is present in the subendothelium and in atherosclerotic plaques; it is in contact with circulating blood in both the electrically damaged model and in the patient with myocardial infarction. Inhibition of the extrinsic tissue factor–dependent coagulation cascade significantly reduced rethrombosis in the electrically damaged vessel. It may well be effective in prevention of rethrombosis of the atherosclerotic vessel as well. This canine model study provides a rationale for studying interventions that inhibit tissue factor thrombosis in atherosclerosis.

The duration of the antithrombotic effect of LACI in this thrombosis model is not known. The animals were killed at the conclusion of the LACI or saline infusion. A natural extension of these experiments would be the monitoring of average and pulsatile flow and cyclic flow variations in animals for a few hours or perhaps a day or two after conclusion of the LACI infusion. For the inhibitor alone to have a clinically significant impact on the incidence of rethrombosis of coronary arteries after successful fibrinolytic therapy, vascular patency must persist after discontinuation of LACI. In the setting of a myocardial infarction, an alternative approach for maintenance of vascular patency would be administration of conventional anticoagulants at the conclusion of the LACI infusion. However, combination of LACI with conventional anticoagulation might negate the attractive characteristic of LACI, that is, minimizing systemic hemorrhagic complications. A second extension of the experiments of Haskel et al. would be to band the electrically damaged femoral artery, creating a stenosis such as occurs in coronary artery disease. A third extension would be the use of other animal models with atherosclerosis.

Fibrinolytic therapy of thrombotic disease is a rapid method of recanalizing an occluded vessel. To achieve maximal therapeutic benefit, the diseased vessel must remain patent after discontinuation of fibrinolysis. Because rethrombosis is a frequent problem, therapies to prevent reocclusion continue to be evaluated in clinical trials and laboratory models.

References


**Key Words** • Editorial Comments • fibrinolysis • reocclusion
Therapeutic fibrinolysis. What should follow?

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