Reduced Tissue Factor Pathway Inhibitor-1 After Pharmacological Thrombolysis
An Epiphenomenon or Potential Culprit in Rethrombosis?

Prediman K. Shah, MD

Thrombosis following plaque rupture is the proximate trigger for abrupt coronary artery occlusion and acute coronary syndromes. Coronary thrombolysis was reintroduced in the early eighties as a means of recanalizing acutely occluded coronary arteries in evolving myocardial infarction, limiting myocardial damage, preserving ventricular function, and improving clinical outcomes. However, it was soon recognized that in addition to the risk of bleeding, thrombolysis failed to achieve robust reperfusion in 25% to 40% of patients, and reocclusion rates of 5% to 15% tended to attenuate the benefits of initial recanalization. Studies demonstrated that pharmacological thrombolysis using plasminogen activators such as streptokinase and tissue type plasminogen activator was followed by a prothrombotic state attributed variously to plasin-induced platelet activation, exposure of clot-bound thrombin, and the prothrombotic effects of products of plasmin action. Thus, rethrombosis following thrombolysis was thought to contribute to both resistance to effective thrombolysis and reocclusion following initial recanalization. These observations provided the rationale for the concurrent use of antiplatelet (aspirin) and antithrombin (heparin) agents with thrombolytic therapy; however, despite their use, thrombolysis failure and rethrombosis/reocclusion rates remained substantial. Failure of aspirin to abolish rethrombosis has been attributed to multiple redundant non-aspirin responsive pathways for platelet activation, and failure of heparin has been attributed to resistance of matrix and clot-bound thrombin exposed after thrombolysis to inhibition by indirect thrombin inhibitors. Thus, other approaches to improving thrombolytic efficacy have included new thrombolytic agents, non-aspirin antiplatelet drugs, and new antithrombins such as low molecular weight heparins, direct thrombin inhibitors, and other anticoagulants. However, either no improvements or only marginal improvements in efficacy and or safety over aspirin and heparin have thus far been demonstrated.

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From the Division of Cardiology and Atherosclerosis Research Center, Burn and Allen Research Institute and Department of Medicine, Cedars Sinai Medical Center and University of California, Los Angeles, School of Medicine, Los Angeles, Calif.

Correspondence to P.K. Shah, MD, Director, Division of Cardiology and Atherosclerosis Research Center, Cedars Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048. E-mail shahp@cshs.org.

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Tissue factor (TF) in atherosclerotic plaques is a critical mediator of arterial thrombosis following plaque disruption; furthermore, circulating tissue factor derived from activated leucocytes may also potentially contribute to arterial thrombosis in absence of frank plaque rupture. Tissue factor is a membrane-bound glycoprotein that initiates blood coagulation by allosteric activation of Factor VII, a serine protease, which then leads to activation of Factors IX and X, ultimately resulting in cleavage of prothrombin to thrombin. Tissue factor pathway inhibitor-1 (TFPI-1) is a serine protease inhibitor with 3 Kunitz-type motifs that blocks Factor VIIa-TF complex and Factor Xa through its first and second Kunitz-type motifs, respectively. Endothelial cells are the major source of endogenous TFPI-1, which circulates in the blood in small quantities in platelets and in truncated forms in association with LDL, HDL, and Lp(a). In addition to its antithrombotic effects, TFPI-1 has been shown to play a protective role in atherogenesis and favorably remodel intimal response to arterial injury. Unlike TFPI-1, TFPI-2 has little anti-TF activity but has recently been shown to have potent inhibitory activities against a broad range of matrix degrading metalloproteinases. Normal arteries express TF predominantly in the adventitia, whereas TFPI-1 is normally expressed predominantly by endothelial cells. In atherosclerotic lesions, TF and TFPI-1 are expressed predominantly by macrophages, and in addition to macrophages, vascular smooth muscle cells and endothelium also express TFPI-1. Enhanced thrombogenicity of lipid-rich plaques is largely attributed to TF-mediated procoagulant activity, which is subject to regulation by TFPI-1. The role of TF and TFPI-1 in the prothrombotic state after pharmacological thrombolysis in man, has heretofore, not been evaluated.

In this issue of Circulation, Ott et al24 provide provocative data showing that pharmacological thrombolysis by alteplase induces a decrease in circulating TFPI-1 in patients with acute myocardial infarction, leading the authors to suggest that such an effect may contribute to rethrombosis after thrombolysis. The authors evaluated a relatively small group of patients receiving reperfusion therapy, using plasminogen activator alteplase in 9 and stenting in 10 patients, during the course of an evolving myocardial infarction. Plasma TFPI-1 levels by immunoassay and cell-associated TFPI-1 in circulating monocytes by flow cytometry were measured before and at various time points after reperfusion. Both cell-associated and plasma TFPI-1 levels fell after pharmacological reperfusion, whereas they rose after mechanical reperfusion with coronary stenting. No change was noted in monocyte TF expression with either mode of reperfu-
sion. The authors also demonstrated in vitro that plasmin resulted in a dose-dependent decrease in cell surface expression of TFPI-1 in human umbilical vein–derived endothelial cells. The authors concluded that plasmin mediated the observed decrease in TFPI-1 in patients receiving alteplase, overshadowing any expected increases from the use of heparin, a substance known to stimulate release of TFPI-1 from endothelium.23 The increase in TFPI observed in patients undergoing mechanical reperfusion with stenting was attributed to unopposed heparin-induced TFPI-1 release. Although authors did not directly measure TFPI-1 proteolysis, their findings of decrease in TFPI-1 after thrombolysis and in vitro data are consistent with previous reports of plasmin-mediated proteolysis and decrease in activity of TFPI-1.25,26 Although it is plausible to then postulate that plasmin-mediated proteolysis of TFPI-1 could create a prothrombotic state due to unopposed TF activity increasing the risk of rethrombosis and reocclusion, data to support this conjecture are missing from this preliminary report. No information regarding efficacy of thrombolysis or evidence of reocclusion is provided although small numbers would preclude a meaningful conclusion from this study. Nevertheless, if the author’s findings can be confirmed in a larger subset of patients where a direct relationship between TFPI-1 decrease and either failure of thrombolysis or reocclusion can be convincingly demonstrated, it would suggest a potentially novel approach for improving efficacy of thrombolytic therapy. Although reduced efficacy of thrombolytic therapy with plasminogen activators and rethrombosis may in part be attributed to loss of natural anticoagulant effect of TFPI-1, it is also likely that other factors such as exposure of bound thrombin, residual stenosis, and shear-induced platelet activation and thrombogenic milieu provided by the residual thrombus and TF-impregnated disrupted atheroma and other unknown factors are also important. Recent observations of Caplice et al27 showing ability of lipoprotein(a), which is elevated as an acute phase reactant during myocardial infarction, to bind and inactivate TFPI-1 adds yet another wrinkle to this story. Experimental observations in canine model of thrombosis have shown improved thrombolytic efficacy when recombinant TFPI-1 was used concurrently with tPA, supporting the overall contention of the authors.28 Because TF-mediated biological processes appear to play a significant role in atherosclerosis, thrombosis, neointimal response to injury, disseminated intravascular coagulation, sepsis, lung injury, and cancer, exploiting the benefits of TFPI-1 may emerge as an attractive therapeutic strategy in a variety of disorders. To this list, facilitation of pharmacological thrombolysis using exogenous excess TFPI-1 or strategies that block plasmin-mediated loss of endogenous TFPI-1 could be a welcome addition. Because thrombosis plays a critical role in cardiovascular pathology and antithrombotic agents in current clinical use have a number of limitations in terms of efficacy and/or safety, the quest for safer and more effective antithrombotic agents continues.7 Time and properly designed additional studies will likely determine whether administering exogenous excess TFPI-1 or enhancing endogenous TFPI-1 activity will emerge as a viable approach or whether the findings reported by Ott et al24 will be relegated simply to a true but unrelated epiphenomenon of uncertain clinical significance.

References


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