Editorial Comments

Recurrent Ischemic Events After Successful Thrombolysis in Acute Myocardial Infarction

The Achilles' Heel of Thrombolytic Therapy

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The use of thrombolytic agents has revolutionized the treatment of acute myocardial infarction, resulting in major reductions in mortality. Despite successful reperfusion in 60–80% of patients, rethrombosis at the site of the previously occlusive thrombus constitutes a major limiting factor in the efficacy of this therapy.

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Although sometimes silent, rethrombosis commonly results in infarct extension and occasionally in death.[1] After thrombolysis with streptokinase, the incidence of reocclusion ranges from 17% to 46%.[2,3] With recombinant tissue-type plasminogen activator (rt-PA), reocclusion rates from 12% to 46% have been reported.[4,5] It is apparent, therefore, that strategies for the detection of patients at increased risk for reclosure are of considerable importance.

To date, coronary angiography has shown greatest promise in identifying patients at increased risk of recurrent ischemic events after thrombolysis. Although pathologic studies have shown that placque rupture occurs in severe preexisting stenoses, usually resulting in total coronary occlusion and consequent myocardial infarction,[6] angiographic studies reveal that severe stenoses are not a prerequisite for myocardial infarction.[7] Angiographic detection of the infarct-related lesion can be obtained by visual recognition of an Ambrose Type II eccentric lesion[8] or quantitation of an "ulceration index."[7] Placque rupture morphology is often not visible immediately after thrombolysis, presumably because of unlysed but inapparent thrombus. Thus, this characteristic morphology of the infarct-related lesion cannot be used immediately after thrombolysis as a marker of the likelihood of subsequent reocclusion.

In 1984, we hypothesized that coronary rethrombosis after streptokinase was related to the luminal size of the residual stenosis.[1] With quantitative coronary angiography, seven of 13 patients (54%) with acute infarction who had undergone successful reperfusion with intracoronary streptokinase developed rethrombosis within 2 weeks if the minimal residual lesion area was less than 0.4 mm^2. None of 11 patients with lumina of more than 0.4 mm^2 developed rethrombosis. Seven of 14 patients with residual lesions causing more than 90% area stenosis had rethrombosis, while none of 10 with lesions of less than 90% area stenosis rethrombosed. A similar conclusion was reached when lesion severity was evaluated by computer-based videodensitometry. These findings were later confirmed by other investigators.[9–13] Intermittent vascular patency during thrombolysis has also been shown to predict a high risk of reocclusion.[14] Thus, the cumulative weight of evidence has led to the conclusion that altered flow dynamics resulting from a severe residual stenosis after thrombolysis is a major factor favoring rethrombosis.

The angiographic demonstration that continued clot lysis often occurs after apparently complete vessel patency has been obtained has added considerable complexity to the issue of "true" severity of the residual lesion. In our initial studies, the minimum lesion cross-sectional area increased 116±34% during the 7–10 days after intracoronary streptokinase thrombolysis.[1] In seven patients, minimum luminal area more than doubled. Similar quantitative data were obtained by Brown and colleagues.[15] Hence, angiographic studies of streptokinase reperfusion show that although thrombolysis continues for days or weeks, the area of the residual lumen immediately after reperfusion can be used to predict patients at high risk for reclosure.

The study from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials with rt-PA in the current issue of *Circulation* is of great interest.[16] This study confirms previous impressions that recurrent ischemic events cannot be predicted by clinical characteristics. Most surprising, how-

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ever, is the finding that these events were not related to any angiographic variables, such as percent diameter stenosis, absolute lesion diameter, angiographically defined thrombus, or stenosis morphology. The overall incidence of recurrent ischemic events in this study (41 of 192, or 21.3%) is similar to those previously reported for streptokinase. However, with rt-PA, these events occurred in 17 patients with a minimum diameter stenosis of 0.6 mm or less (a previous predictive value for continued normal perfusion status derived from streptokinase studies)[13] and in patients in whom the residual diameter stenosis was as low as 55%. How can such disparate findings between streptokinase and rt-PA be reconciled?

The explanation will probably be found to relate to fundamental differences in the physiologic effects of the thrombolytic agents used. To initiate thrombolysis, agents introduced into the circulation activate plasminogen at two different sites: soluble plasminogen in the circulating blood and fibrin-bound plasminogen in the thrombus. Agents that are relatively fibrin selective, such as rt-PA, have a high ratio of affinity for surface-bound plasminogen versus circulating plasminogen.[17] Nonfibrin-selective agents, such as streptokinase, characteristically cause a major degradation of plasma fibrinogen and proteolysis of other plasma proteins and blood-clotting factors (V and VIII).[18] A major controversy now exists regarding the merits of fibrin-selectivity as a characteristic for an ideal thrombolytic agent. Although fibrin-selectivity was originally hypothesized to result in decreased bleeding complications, invasive trials of thrombolysis in acute myocardial infarction have not confirmed this hypothesis. If invasive procedures are avoided, the incidence of bleeding with either nonfibrin-selective or fibrin-selective thrombolytic agents is low.[19,20] Thus, Marder and Sherry have argued that the primary cause of bleeding after thrombolysis is lysis of hemostatic plugs and the concomitant administration of heparin, with the induced coagulation defect playing only a minor role.[18,21]

Rethrombosis rates, although initially believed to be higher with fibrin-selective agents, are probably similar to those seen with nonfibrin-selective drugs. Although a rough inverse relation should exist between the length of the plasma half-life and rethrombosis,[18] direct comparison studies are not available. Despite the shorter half-life of fibrin-selective agents presumably promoting rethrombosis, other confounding factors may supervene.[22] Increased fibrinogenolysis produced by nonfibrin-selective agents may aid in resisting rethrombosis by a decreased plasma viscosity and diminished red blood cell clumping, thus causing increased flow velocity across residual stenotic lesions.[23] Hypofibrinogenemia may also decrease the likelihood of rethrombosis by interfering with the platelet-fibrin mesh.[24]

Multiple additional mechanisms likely play a major role in determining continued patency versus rethrombosis. A thrombogenic stimulus usually persists after thrombolytic therapy. Residual partially lysed clot with its surface-bound thrombin can act as a stimulus for further platelet aggregation and new fibrin formation.[11] Even total thrombolysis will reexpose the original thrombogenic atherosclerotic plaque fissure.[1,6] Vasoactive agents released from ongoing clot lysis (thrombin and thromboxane) may paradoxically tend to reactivate the coagulation cascade.[25,26] Activated plasmin may produce a state of hypercoagulability and platelet activation.[27]

The effect of thrombolytic agents on platelet activation may vary, not only with the degree of fibrin-selectivity but also with the solubilizing agent.[28] Because fibrinogen is a cofactor for ADP-induced platelet aggregation, the degree of fibrinogenolysis may variably affect platelet function.[29] Activation of plasminogen bound to platelets decreases the platelets' response to various agonists.[30] Platelet disaggregation resulting from plasminogen-induced dissolution of such adhesive proteins as thrombospondin, fibronectin, and fibrin may disrupt the interplatelet matrix fundamental to rethrombosis.[24] In a recent in vitro study, Vaughan and Loscalzo reported that although t-PA, streptokinase, and urokinase all produced significant fibrinogenolysis by 5 minutes, only t-PA resulted in disaggregation of ADP-induced platelet aggregates.[31]

The role of heparin in preventing recurrent ischemic events after thrombolysis is also complex. Initial clinical experience with streptokinase suggested that rethrombosis often occurred when heparin was temporarily discontinued to achieve hemostasis after catheterization. Recent evidence indicates that heparin binding to activated platelets during thrombolysis may enhance platelet hyperaggregability contributing to an increased risk of bleeding.[32] Most clinical trials have continued to use heparin to prevent rethrombosis. This practice is not particularly successful, and there is increasing concern that standard heparin preparations may contribute to both thrombosis[17] and increased bleeding complications.[33]

Biochemical markers may, in the future, be helpful in predicting rethrombosis. A reduced fibrinolytic capacity due to increased plasma levels of a rapid inhibitor of t-PA may be important in the pathogenesis of infarction[34] and in the development of reinfarction.[35] The role of this inhibitor in rethrombosis has not been determined. Thrombin–antithrombin-III (TAT) complex levels have been shown to be an early predictor of reocclusion.[36] Fibrinopeptide A (FPA) appears to reflect the success or failure of thrombolytic recanalization.[37] In patients with lysis but subsequent reocclusion, FPA initially falls and then rises markedly. An interaction between heparin and FPA levels, however, complicates the interpretation of these levels in clinical practice.[38]

These proposed mechanisms for rethrombosis have led to a variety of approaches for its prevention.

Administration of Vasodilators

Although nitrates and calcium antagonists are commonly prescribed medications after thrombolytic therapy, the problem of rethrombosis remains. Preliminary data suggest that combined intracoronary prostaglandin E_1 and streptokinase may improve the initial recanalization rate.[39] Whether such therapy decreases rethrombosis merits its evaluation.

Alterations in Thrombolytic Dosage Regimens or Drug Composition

Initial attempts to decrease rethrombosis focused primarily on changes in drug administration. Gold et al[5] reported that, combined with a large initial dose, a maintenance infusion of rt-PA could greatly reduce the reocclusion rate.[5] Subsequently, however, these investigators reported that a reduced-dose rt-PA infusion was associated with a reocclusion rate of more than 40%.[40] Although increased doses of nonfibrin-selective agents might decrease the incidence of rethrombosis, rt-PA doses of more than 100 mg are contraindicated because of a higher incidence of intracerebral bleeding. New genetic engineering approaches to create rt-PAs with longer intrinsic thrombolytic activity appear to be a promising avenue for further investigation.[41]

Anticoagulants and Antiplatelet Agents

Results from the International Study of Infarct Survival show that aspirin combined with streptokinase markedly enhances survival, perhaps mediated, in part, through decreased rethrombosis.[42] Antibodies to the platelet IIB/IIIA receptor may decrease rethrombosis by reducing platelet reactivity.[43] Administration of a low molecular weight heparin fraction with high antithrombin affinity may also be a promising approach to this problem.[44]

Percutaneous Transluminal Coronary Angioplasty

Initial data suggested that percutaneous transluminal coronary angioplasty might be beneficial in decreasing rethrombosis.[45] The TAMI and TIMI trials, however, have shown that immediate angioplasty is associated with increased acute coronary occlusion.[46,47] Although conventionally ascribed to hemorrhagic dissection, the evidence is not overwhelming. Recent studies from our laboratory have suggested that angioplasty of unstable coronary lesions or residual lesions several days after thrombolytic therapy may lead to severe vasospasm of small coronary resistance vessels not visible by angiography, resulting in widely patent epicardial coronary vessels with slow or no contrast washout.[48] Vasoactive metabolites released from platelets activated by coronary dilation during acute angioplasty might effect a poor result from a similar mechanism.

The evidence thus suggests that the fibrin-selective and nonfibrin-selective thrombolytic agents variably predispose to rethrombosis via different mechanisms. This information is certain to contribute additional fuel to arguments presently existing regarding the choice of thrombolytic agents for the treatment of myocardial infarction. The dilemma of how to prevent rethrombosis without causing an unacceptably high increase in hemorrhagic complications thus remains the Achilles' heel of thrombolytic therapy.

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