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CME CREDIT HOURS

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Reperfusion for acute myocardial infarction: 1997 and beyond

Although thrombolytic therapy and angioplasty have decreased the mortality rate in acute myocardial infarction (MI), thrombolytic therapy fully opens the blocked artery in only half of cases, and primary angioplasty is impractical for most patients.

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Research into the formation of clots has shown that standard thrombolysis attacks only one arm of the clotting mechanism, and may miss the primary target—platelet aggregation. However, a new class of drugs that attack this problem, the platelet glycoprotein IIb/IIIa inhibitors, may usher in a new era of treatment for acute MI. Most likely, the optimal thrombolytic therapy will be a cocktail of several thrombolytic, antithrombotic, and antiplatelet agents, each of which attacks different pathways of clot formation.

THE SOBERING FACTS ABOUT THROMBOLYSIS AND REPERFUSION

The large-scale Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial, completed in 1993, confirmed something we long suspected intuitively: in acute myocardial infarction, the mortality rate is lower, and other clinical outcomes better, in patients in whom complete coronary blood flow is restored quickly than in patients who do not achieve complete reperfusion.[1]

In GUSTO patients who underwent angiography at 90 minutes, the mortality rate in the first 24 hours, when half the deaths in myocardial infarction occur, was 0.7% in patients with complete reperfusion (grade 3 by the criteria of the Thrombolysis in Myocardial Infarction [TIMI] trial[2]) vs threefold higher in patients with lesser grades of reperfusion. The survival difference was still significant 5 years later.[3] In fact, so strong was the effect of TIMI grade on survival that we could accurately predict the mortality rate in each of the four GUSTO treatment groups on the basis of how many patients in each group achieved TIMI grade 3 flow.[4]

Yet GUSTO pointed out a sobering fact. Even in the group that received an accelerated regimen of tissue plasminogen activator (t-PA)—the best thrombolytic regimen devised to date—only 54% of patients achieved TIMI grade 3 flow (compared with only approximately 30% of patients in the other three treatment groups).[1] We must do better. But how?

PRIMARY ANGIOPLASTY: A REALITY CHECK

Several studies suggested that angioplasty, performed within 60 minutes of coming to the emergency room, can restore TIMI grade 3 flow in 85% to 90% of patients, and reduce the mortality rate by up to 70% compared with thrombolysis.[5–7]

These findings were probably overly

optimistic, coming from relatively small trials without sample size calculations or rigorous adjudication of outcomes. A recent retrospective study found no difference in the mortality rate between patients who underwent primary angioplasty or thrombolysis, either in the hospital or at 3 years.[8] We recently completed a large prospective trial (GUSTO-IIb) comparing angioplasty vs an accelerated t-PA regimen, and have submitted the results for publication.

Most cardiologists do believe that angioplasty is more effective than thrombolysis—*if* the hospital is equipped to perform it (85% are not), *if* it can be performed within 90 minutes of the patient entering the hospital (the nationwide average is 2 hours), *if* the team is experienced, and *if* the patient has the right type of lesion. This "reality check" suggests that most patients with acute myocardial infarction would be well served with thrombolysis.

In the future, we will attempt to intervene higher up in the coagulation cascade and block thrombin generation

BUILDING A BETTER PLASMINOGEN ACTIVATOR

Although t-PA is the body's own plasminogen activator, perhaps a bioengineered analogue would lyse clots more effectively. Several such agents are undergoing clinical trials; of these, reteplase (r-PA) has been best studied and was recently approved by the Food and Drug Administration. In clinical trials, r-PA appears slightly more effective than t-PA.[9–11] However, its real advantage is that it is cheaper and easier to give (two boluses of 10 million units each, 30 minutes apart). Other new plasminogen activator agents that are also given via bolus administration are novel plasminogen activator (n-PA) and triple site-directed mutant (TNK).

TAKING ANOTHER LOOK AT CLOTS

Most myocardial infarctions start when a plaque inside a coronary artery ruptures, exposing the subendothelial matrix. Platelets aggregate in the lesion, forming a "white" clot. A fibrin-thrombin ("red") clot then forms on top of the white clot. All of our efforts to date have focused on dissolving the red clot, and not the underlying white clot.

But by ignoring the white clot, we may be missing the target. In fact, standard thrombolytic therapy, which does not touch the underlying, platelet-rich white clot, may actually be self-defeating: by lysing fibrin, standard thrombolytic therapy frees thrombin, the most potent platelet aggregation agonist there is. And thrombin stimulates conversion of more prothrombin into thrombin. To add insult to injury, the aggregated platelets secrete plasminogen activator inhibitor (PAI-1), blocking the effect of the fibrinolytic drug (**FIGURE**). All of these factors may explain thrombolytic therapy's disappointing patency rate up to now.

TOWARD THE IDEAL THROMBOLYTIC REGIMEN—COMBINATION THERAPY

I believe we can greatly improve the effectiveness of current thrombolytic therapy by including powerful drugs that inhibit the glycoprotein IIb/IIIa receptor, the final common pathway of platelet aggregation. Such drugs, which break up white clots, have already been shown to reduce the rate of restenosis when given during angioplasty,[12,13] and trials are in progress in thrombolysis.

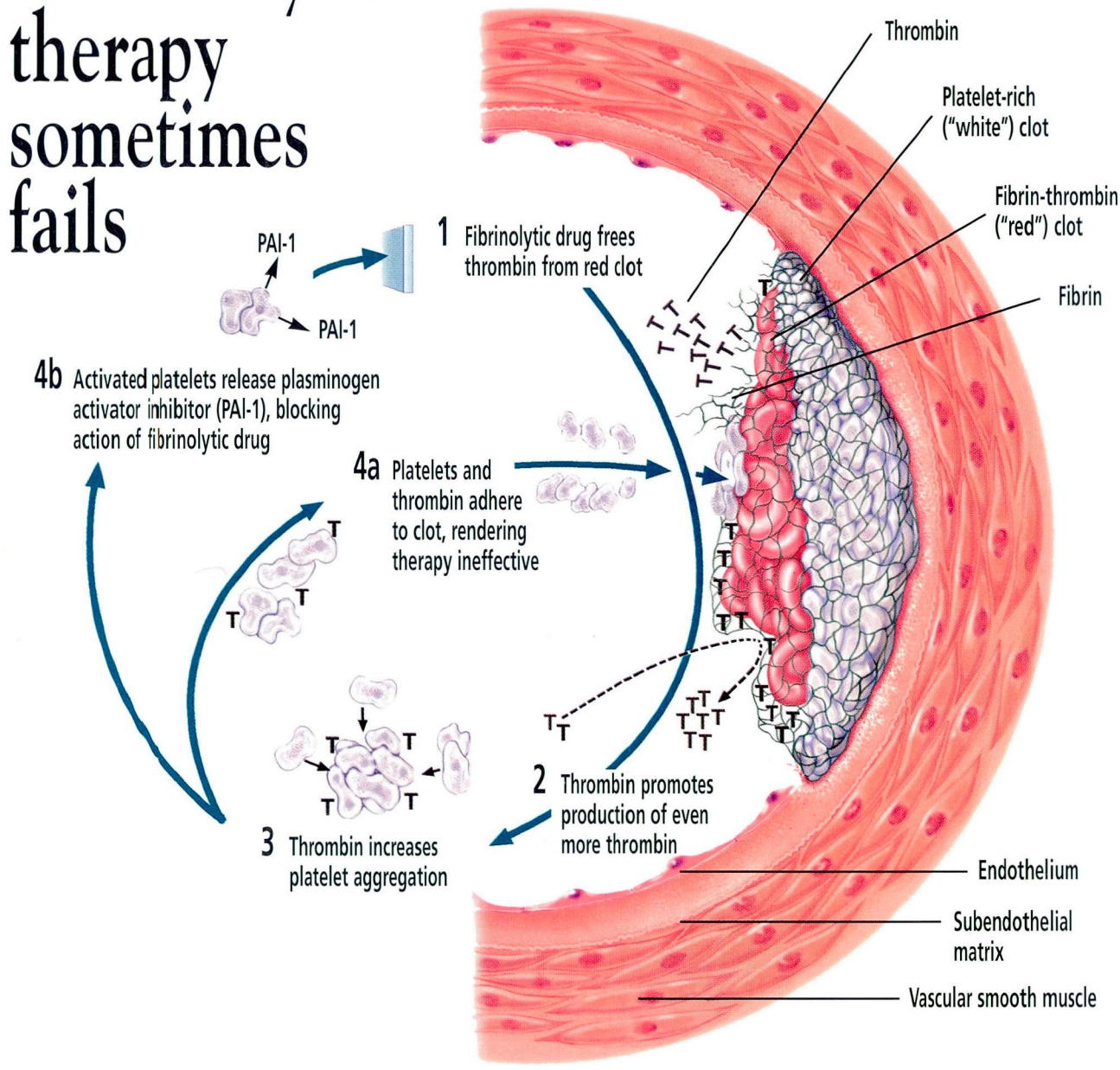
The ideal thrombolytic regimen would also include a next-generation fibrinolytic agent such as r-PA or TNK, but in a lower dose than used now, to avoid the risk of hemorrhagic stroke that plagues these agents.

Also in the regimen will be a thrombin inhibitor. Heparin, introduced in 1906, inhibits free thrombin but not the thrombin bound in clots. Surprisingly, we still do not know how to use it effectively; whereas we believed the optimal heparin dosage would increase the activated partial thromboplastin time (aPTT) to 90 to 100 seconds, in the GUSTO-I trial we found that optimal effect on mortality occurred in the range of 50 to 70 seconds.[14]

Hirudin, derived from leech saliva, inhibits both circulating and clot-bound thrombin and is therefore much more powerful

FIGURE

Why thrombolytic therapy sometimes fails



Most myocardial infarctions start when a plaque inside a coronary artery ruptures, exposing the subendothelial matrix. Platelets aggregate in the lesion, forming a "white" clot. A fibrin-thrombin ("red") clot then forms on top of the white clot. Standard thrombolytic therapy, which does not touch the underlying, platelet-rich white clot, may actually be self-defeating: by lysing fibrin it frees thrombin (the most potent platelet aggregation agonist). And thrombin stimulates conversion of more prothombin to thrombin. To add insult to injury, the aggregated platelets secrete plasminogen activator inhibitor (PAI-1), blocking the effect of the fibrinolytic drug.

than heparin. However, neither heparin nor hirudin inhibits thrombin generation. When we compared the two thrombin inhibitors in the GUSTO-IIa trial, hirudin had a statistically significant benefit in the short term, but less so in the long term.[15]

Therefore, in the future, we will attempt to intervene higher up in the coagulation cascade and block thrombin generation. In the works are factor Xa inhibitors, tissue factor pathway inhibitors, and factor VIIa mimetics.

In the end, however, the best strategy for treating myocardial infarctions will be to prevent them in the first place, by lowering lipid levels, smoking cessation, antihypertensive treatment, and other measures. ■

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