Dynamics of Coronary Thrombolysis and Reocclusion

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Summary: The dynamics of coronary thrombosis and reocclusion may seem straightforward, but in actuality they are complex and incompletely understood. The pathobiology of coronary thrombosis begins with the development of the atherosclerotic plaque. The initial step in the process, endothelial cell dysfunction, alters vascular thromboresistance. Plaque erosion or overt disruption is followed by platelet adherence, aggregation, and thrombin generation that stimulates the conversion of soluble fibrinogen to fibrin. Thrombolytic therapy, although able to dissolve a high proportion of occlusive thrombi, creates a procoagulant environment by generating plasmin which, in turn, activates platelets and generates thrombin, increasing the likelihood of vessel reocclusion. Thrombin is therefore considered an important target for research, and several thrombin inhibitors have been developed. Antiplatelet agents such as aspirin are currently employed to prevent reocclusion following thrombolytic therapy; however, several new and more potent platelet antagonists are being investigated with considerable enthusiasm.

Key words: thrombolysis, reocclusion, atherosclerosis, platelets, thrombogenesis

The open vessel hypothesis is a conceptual framework that has paved the way for clinical success. The early work of Blumgart¹ was followed by the observations of Braunwald and Moroc² concerning the duration of coronary occlusion and its correlation with infarct size, and by the widely quoted work of Reimer and Jennings³ revealing the time-dependent "wave front phenomenon" of myocardial necrosis.

The field has come a long way toward developing treatments for acute myocardial infarction (AMI) but has a distance to travel, particularly in regard to providing potentially life-saving therapy for all patients who are potential candidates. In terms of the dynamics of coronary thrombolysis and reocclusion, there is a number of components that must be considered, including atherogenesis, thrombogenesis (collectively referred to as atherothrombosis), and inflammation (acute, chronic). Other important considerations include the dysfunctional endothelial cell; the development of the vulnerable plaque; and systemic factors that will, at times, "shift the balance" toward thrombosis (Fig. 1).

A normal coronary artery has a large lumen through which blood can flow and an endothelial surface that can protect against nonphysiologic clot formation (thromboresistance); it can dilate or constrict according to need. Unfortunately, humans have a tendency to develop atherosclerosis; however, the rate of development and specific features or characteristics of the plaque differ significantly from person to person.

Individuals with soft "vulnerable" plaques are at risk for thrombotic coronary events, while those with hard/fibrous "nonvulnerable" plaques, although likely to develop symptoms of angina from progressive luminal narrowing, less often experience acute coronary occlusion.

Why do some individuals with plaque disruption develop occlusive thrombosis while others do not? The answer is partly based on the depth of the plaque rupture, because in most instances the thrombogenic components are found deep within the plaque. Some individuals, however, are predisposed to forming thrombi even with minimal plaque disruption; tobacco smokers are an example. We have shown that there are increased numbers of platelets signaling monocytes in individuals with stable coronary disease, long before they experience unstable angina or an AMI (Fig. 2); this observation suggests that inflammation and thrombosis are closely linked. Moreover, in patients with atherosclerosis, platelets circulate in an activated or highly activatable form. Platelets should only activate in the presence of an abnormal surface and where, teleologically speaking, they are needed to participate in physiologic hemostasis. In atherosclerosis, however, the situation is quite different.

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Several studies have used coronary angiography as a means to evaluate reperfusion strategies, including thrombolysis and primary angioplasty in patients with AMI, correlating mortality with Thrombolysis in Myocardial Infarction (TIMI) flow grade 1. TIMI grade 3 flow is thought to represent normal physiologic flow and, although there may be some limitations with this grading scale, it has provided important insights toward developing new therapies. Major angiographic studies have shown that the greater the proportion of patients with TIMI grade 3 flow, the lower the mortality rate. However, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)⁴ data also show that, during the first 4 h, the angiographic flow grade correlates poorly with early mortality (Fig. 3). This is, in part, a function of treatment delay and reperfusion delay. It may also reflect a "nonsalvageable" myocardium and, perhaps, is influenced by the occurrence of early cardiac rupture events.

During thrombogenesis, platelets and fibrin interact. The fibrin component of the clot provides a rationale for considering fibrinolytic or thrombolytic therapy as a means for dissolving the clot, restoring blood flow to the myocardium, salvaging myocardium, reducing infarct size, and saving lives. By dissolving the clot, thrombolysis itself sets the stage for reocclusion by "unmasking" the original substrate (ruptured plaque). During the last 5 to 10 years, attention has focused on thrombin, the major catalytic enzyme for all thrombotic processes, whether hemostatic or pathologic. Thrombin is the most potent platelet activator known and converts fibrinogen to fibrin. Thrombin is also a major factor in reocclusion and largely determines the prothrombotic potential of thrombolytic agents. The plasmin generated by thrombolytic therapy, in turn, generates thrombin by several pathways. Thus, as thrombolysis releases thrombin from within the clot, the thrombolytic process itself generates new thrombin by procoagulant mechanisms (Fig. 4).

Staphylokinase is a thrombolytic agent with greater fibrin specificity than tissue plasminogen activator (TPA) and other

thrombolytics. By nature of its fibrin specificity, staphylokinase generates less circulating plasmin, which then causes less activation of platelets, direct prothrombin to thrombin catalytic action, and intrinsic coagulation cascade activation. Although the clinical implications of this observation are unknown, we must consider unique properties of the thrombolytic agents themselves when attempting to achieve and maintain arterial patency.

Over the years we have employed various pharmacologic means to inhibit thrombin and have come to realize that the key to effective treatment is to prevent thrombin generation. While studying hemophilia in our laboratory, we identified an important interaction between the extrinsic and intrinsic coagulation cascades, suggesting that tissue factor is a primary determinant of both hemostatic clots and pathologic thrombi. This observation opens opportunities for the development of new anticoagulants, including tissue factor pathway inhibitors, low molecular weight heparins, and direct, selective factor Xa antagonists.

Another way to prevent reocclusion is to inhibit the platelet itself, which is further activated by thrombolytics in the process of clot dissolution. With antiplatelet agents such as aspirin, the death rates from AMI can be reduced by 25 per 1,000 patients treated, recurrent MI can be reduced by at least one third, and stroke by up to one half. Thus, antiplatelet therapy represents a standard of care for patients with AMI and probably offers benefit by preventing coronary reocclusion and other intravascular thrombotic events. Its anti-inflammatory potential probably is important as well. Once more is known about platelet-platelet interactions, we undoubtedly will be able to take a step beyond aspirin. Regardless of the mechanism for activation of the platelet, whether it be shear stress or biochemical mediators, each platelet communicates with an adjacent platelet through a particular receptor known

FIG. 1 Dynamics of thrombolysis and reocclusion.

FIG. 2 Inflammatory and prothrombotic potential in coronary artery disease: Monocyte-platelet aggregates. ADP = adenosine diphosphate, Epi = epinephrine, TRAP = thrombin receptor agonist peptide. ■ = Controls, ■ = patients. Cardiovascular Thrombosis Research Center, 1997.

as the glycoprotein-IIb/IIIa receptor. Inhibitors of this receptor have greater antiplatelet potential than aspirin. Adenosine diphosphate (ADP) receptor antagonists, including ticlopidine and clopidogrel, as well as purine receptor antagonists may also provide a unique approach to platelet inhibition.

To meet individual needs of a growing number of patients, we must ascertain why the mortality rates observed in recent clinical trials are on the rise. An aging population is likely responsible, raising important questions about ideal treatment strategies based on age and other high risk patient characteristics.

Discussion

Rawles: I would like to challenge the open artery hypothesis as you've stated it. I would accept that the benefits of thrombolytic treatment are mediated by means of having an open infarct-related artery, but I would draw the line at saying that the benefit is therefore related to myocardial salvage. If you go back to the work of Reimer, by 6 hours after coronary occlusion there is no myocardial salvage. Even after 2 hours, the amount of myocardial salvage is trivial. From the pooled data in the FTT overview, it is clear that patients *do* benefit by having the infarct-related artery opened up far beyond 6 hours, up to perhaps 24 hours. So we have to invoke some other mechanism of benefit. What we have seen in the large hospital-based trials of thrombolytic treatment is reduction of mortality by two to three percent. To a very large extent, these other mechanisms have to do with the open artery resulting in better electrical stability of the infarct and better healing to prevent remodeling. We really haven't seen myocardial salvage to any extent in hospital-based trials.

Becker: I agree with your statement. The open vessel hypothesis has been expanded beyond the original description to

include "time-dependent" and "time-independent" phenomena. The time-dependent phenomenon is based predominately on myocardial salvage. One of the challenges in humans (as compared with animal models) is trying to determine when "time zero" (vessel occlusion) occurs. I believe that in some cases there is a greater amount of time for salvage than we perceive, knowing that up to 75% of patients actually have preinfarction angina as one of their warning signs. I also agree that the KFT ventricular ejection fraction is not a sensitive marker of myocardial salvage. But we certainly know that the remodeling process is favorably influenced by successful reperfusion.

Hennekens: Having an open artery is certainly good for the patient, and the earlier it opens, the greater the survival benefit. However, it's not the whole story, since there are clear benefits up to 12 h after onset of treatment and, as has been suggested, maybe even up to 24 h. Based on both your comments, the combination of TPA providing early patency and greater fibrin specificity/short half-life plus streptokinase providing a delayed onset and sustaining Grade 3 flow should have had significant effect on mortality. Yet, the GUSTO-1 found no incremental mortality benefit for the combined therapy with TAP and SK over either TPA alone, or SK alone, and I wonder what your thoughts are on that?

Becker: When the trial was designed there were compelling data in favor of combination therapy. As you mentioned, the hypothesis being tested was to use a very rapid acting thrombolytic to open the vessel and a delayed, or more "sustained-effect" thrombolytic to keep the vessel open. The question in my mind then and now is proper dosing, and whether thrombolytics are actually able to keep vessels open. The evidence would suggest that the available agents can not, supporting on-going investigation for adjunctive therapies to enhance and maintain patency.

Rawles: Dr. Zweifler mentioned the recent decline in coronary heart disease mortality. One reason can't be entirely credited to treatment related to developmental factors. We know from Barker's work in Britain that nutrition, even in utero, may affect the later occurrence of coronary artery disease. So we may be seeing a cohort of adult patients in whom

FIG. 3 24-hour mortality in GUSTO-1. ■ = tissue plasminogen activator, ▲ = streptokinase, ◆ = tissue plasminogen activator + streptokinase. Adapted from Ref. No. 1.

Atherogenesis

- Endothelial cell dysfunction
- Inflammation
- Vulnerable plaque development

Thrombogenesis

- Plaque rupture
- Plaque thrombogenicity
- Platelets
- Thrombin

Thrombolysis

- Biochemistry

Reocclusion

- Thrombogenic substrate
- Prothrombotic potential of plasmin
- Inadequate suppression of thrombin and platelets

FIG. 4 Dynamics of thrombolysis and reocclusion.

coronary heart disease is less prevalent now. Moreover, here is other evidence that weighs against a significant therapeutic effect. Studies have failed to show the expected fall of case fatality rate for acute myocardial infarction. From the time of onset of the attack in the community, the case fatality rate is about 50% and it hasn't reduced for the past 2 to 3 decades. The reason is that two thirds or three quarters of the deaths from acute infarction occur outside the hospital. I believe that this is the main reason that the thrust of today's meeting should be on time, because it's all very well to improve treatment once patients get into hospital, or with TPA which acts a few minutes faster; however, most of the deaths are taking place out in the community. If we are to make any real impact on mortality we have to start the whole process very much earlier and preferably in the community.

Becker: I don't want to give the impression that adjunctive therapies can only be given in hospital, when in fact these agents could likely be given in the field. We are developing intravenous and oral antiplatelet agents that perhaps Dr. Newby could comment on later. Some are very potent platelet antagonists that could be given in the field with the aim of enhancing reperfusion and maintaining vessel patency.

Hennekens: I want to support Dr. Rawles' point regarding the need for more research about early childhood influences on cancer and coronary artery disease. As regards to cancer, nutritional influences, especially on breast cancer, are crucial. With respect to the decline in coronary disease, as Dr. Zweifler suggested, cigarette smoking rates have gone from about 50% to less than 30% over the last several decades. Cholesterols have gone from about 220 mg/dl to below 210

mg/dl on average and we now have a higher proportion of people with hypertension diagnosed and treated effectively. All of those changes are likely related to a decline in incidences of acute myocardial infarction. With regard to the treatment of patients, hospital mortality has gone from 20–30% to 5–10%. It should also be noted that while there have been remarkable gains, the decline may be leveling off, and there's some debate about whether mortality rates are on the rise. If we look at young people today in the U.S., we see that, for the first time, their smoking rates are higher than their parents' were at their age, they are heavier, and they are less physically active. Thus, we have made major gains in prevention and treatment that have reduced mortality from cardiovascular disease in middle-age, but there are alarming trends in risk factors among young people that will likely lead to rises in future rates of mortality from cardiovascular disease.

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