Cardiovascular controversies

Evidence for a pivotal role of platelets in vascular reocclusion and restenosis

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Keywords: Restenosis; Platelets; Coronary angioplasty; Thrombin

Reocclusion and restenosis continue to be the major clinical complications following emergency and elective coronary interventions. Reocclusion ultimately occurs in more than 25% of patients after successful thrombolysis for acute myocardial infarction [1] and may have major adverse consequences, ranging from mortality to compromised cardiac function. After percutaneous transluminal coronary angioplasty (PTCA), the risk associated with acute occlusion leading to myocardial infarction, emergency repeat PTCA, or coronary bypass surgery, may occur in up to 8% of patients [2]. Even more frequent and to date resistant to therapy is the possibility of restenosis, which occurs in 30–40% of patients after PTCA and requires an additional percutaneous intervention or bypass operation within the following year.

Substantial evidence directly implicates platelets in reocclusion and restenosis. In fact, current clinical data suggest that platelets represent the most beneficial therapeutic target to reduce the risk of reocclusion and restenosis. In line with this "controversy series" thrombin is being considered the alternative to platelets in the pathogenesis of vascular reocclusion and restenosis. By virtue of its capacity to mediate fibrin formation, platelet activation and cellular migration and proliferation, thrombin undoubtedly is an important player in reocclusion and restenosis. Nevertheless, thrombin inhibitors have yet to match the dramatic effects of platelet antagonists in patients.

Role of platelets in reocclusion

Several mechanisms involve platelets in reocclusion following PTCA or thrombolytic therapy, particularly if removal of the original thrombus is incomplete. (1) The capacity of residual thrombus to support platelet deposition is well-established in experimental animal models and in humans. (2) Residual thrombus also may generate high shear stress which can activate and aggregate platelets. (3) Activated coagulation proteins, such as thrombin and Factor Xa, which are bound to fibrin, become exposed after thrombolysis, and can lead to additional platelet activation and aggregation. (4) Thrombolytic agents may also play a role in platelet-mediated reocclusion as t-PA can enhance platelet aggregability. High concentrations of plasmin can directly activate platelets. Based upon these mechanisms, platelet antagonists might have a significant beneficial effect on thrombolytic therapy. This prediction was supported by the ISIS-II Trial in which patients received placebo, streptokinase, aspirin, or aspirin in combination with streptokinase [3]. In this clinical trial, patients receiving streptokinase + aspirin had a significantly lower mortality and lower rate of recurrent infarction than patients who received streptokinase alone. A new generation of more powerful platelet antagonists than aspirin is emerging. These drugs block platelet aggregation by inhibiting the function of GPIIb-IIIa. The possibility that these GPIIb-IIIa antagonists might have even more beneficial effects than aspirin has been borne out in the Initial trials of the monoclonal antibody, c7E3. In a pilot clinical study (TAMI 8), 37 patients admitted for myocardial infarction received c7E3, in addition to t-PA [4]. By angiography, the infarcted vessel was patent in 92% of these patients compared to 56% (5/9) of patients not receiving the platelet blocker. Furthermore, initial results with Integrelin, a peptide-based antagonist of GPIIb-IIIa, demonstrate a marked potentiation of infarct vessel patency when used in conjunction with accelerated t-PA [5]. These results contrast with the experience using the potent thrombin inhibitor,
hirudin, in the TIMI 9B trial. This agent was not more potent than heparin in reducing the rate of primary events (death, myocardial infarction, congestive heart failure), or the rate of recurrent myocardial infarction. Interestingly, intravenously or subcutaneously administered heparin has not been shown to reduce mortality in acute myocardial infarction in conjunction with thrombolytic therapy. Thus, the greater efficacy of the more potent platelet antagonists on reocclusion has not yet been matched by potent thrombin inhibitors.

Role of platelets in restenosis

Numerous experimental studies, including ones with animals rendered thrombocytopenic, have highlighted the role of platelets in restenosis. Balloon angioplasty disrupts the continuity of the endothelium, exposing adhesive substrates to circulating platelets. Platelet adhesion is frequently followed by secretion of chemokines and mitogens, such as PDGF, TGFβ and bFGF, which induce smooth muscle cell migration and proliferation. Early clinical trials, testing agents such as aspirin, ticlopidine, and thromboxane A2 inhibitors, failed to demonstrate beneficial effects of platelet antagonism on restenosis. The clinical trial (EPIC) of c7E3, however, suggested a significant beneficial effect of platelet antagonists on clinical restenosis after angioplasty, c7E3, administered as a bolus plus a 12-h infusion, not only had a significant effect on the immediate events following high-risk coronary angioplasty [6], but also reduced the number of ischemic events at 6 months by 26%, suggesting a long-term benefit in clinical restenosis [7]. Thus, 7E3 was the first drug to have a significant impact on restenosis in humans. It should be noted that c7E3 crossreacts with integrins on cells other than platelets and it is possible that its beneficial effects on restenosis relate to its cross-reaction with αvβ3 on endothelial or smooth muscle cells. While this uncertainty remains, thrombin inhibitors have been thus far unsuccessful in affecting restenosis in clinical trials. In the HELVETICA trial hirudin produced a significant reduction in the rate of major cardiac events within the first 96 h after angioplasty compared to heparin, but there was no reduction in the rate of cardiac events at 7 months or in the rate of angiographically verified restenosis [8].

Why platelet antagonism may be more effective than thrombin inhibition

It has been argued that thrombin is the major activator of platelets in vivo such that inhibition of thrombin alone may be adequate to prevent platelet involvement in acute thrombotic events, such as reocclusion, or in longer term events, such as restenosis. There are several reasons why this supposition may be an erroneous oversimplification.

First, platelet agonists, other than thrombin, such as ADP, epinephrine, thromboxanes, and shear stress can activate and aggregate platelets. Thus, thrombin-independent mechanisms may contribute to platelet activation in vivo. Second, thrombin is an extremely potent inducer of platelet activation and blood coagulation. Even limited escape of thrombin activity from inhibition may be problematic. Third, the role of platelets in restenosis may be independent of their activation by thrombin. If adhesion of platelets to exposed subendothelium is adequate to trigger their functional contribution to restenosis, thrombin inhibition would have little beneficial effect.

Conclusions

In this commentary, we have emphasized the role of platelets vs. thrombin in reocclusion and restenosis. Realistically, optimal therapy for reocclusion and restenosis may very well require inhibition not only of platelet activation but also of thrombin activity. Indeed, we have previously demonstrated such additivity [9]. However, optimal regulation of thrombin may require agents which prevent its generation rather than blocking its activity. Thus, optimal therapy may require early intervention into the coagulation system, coupled with blockade of platelet function.

References