Adjunctive infusion of antithrombin III during percutaneous transluminal coronary angioplasty

Periprocedural thrombus formation is not only responsible for one of the most serious complications of percutaneous transluminal coronary angioplasty, acute thrombotic occlusion of the coronary artery, but has also been postulated as the initial trigger of pathophysiological mechanisms leading to restenosis⁴¹. The latter hypothesis is based on experimental findings showing that thrombin activation stimulates mitogenesis and cell growth in cultured fibroblasts and smooth muscle cells. Furthermore, empirical data in patients with unstable angina, in whom coronary thrombus formation following initial plaque disruption is frequently present, have shown a worse acute outcome and increased restenosis rates after percutaneous transluminal coronary angioplasty. For these reasons, antithrombotic therapy with heparin and antiplatelet agents have become established as standard treatment for patients undergoing percutaneous transluminal coronary angioplasty.

Heparin is an effective antithrombotic agent that primarily acts by catalyzing the inactivation of thrombin and activated factor X by antithrombin III. Therefore, heparin needs the plasma protein antithrombin III to function as an inhibitor of thrombin. Systemic or local antithrombin deficiency might limit the antithrombotic effectiveness of heparin during percutaneous transluminal coronary angioplasty.

Indeed, depletion of antithrombin III activity was demonstrated repeatedly in patients with unstable angina by several authors and is responsible for reduced efficacy of heparin resulting in acute thrombus formation after percutaneous transluminal coronary angioplasty⁴². Accordingly, Schächinger et al.⁴³ investigated whether an intracoronary infusion of antithrombin III during percutaneous transluminal coronary angioplasty might reduce acute thrombotic occlusion. The result failed to indicate a significant reduction. These authors therefore felt that antithrombin III would not play an important role in this setting and that platelet activation and aggregation were mainly responsible for local thrombus formation and thrombotic occlusion after percutaneous transluminal coronary angioplasty. Unfortunately, patients were not investigated as regards late clinical outcome in this study.

In the present issue, Grip and co-workers⁴⁴ investigated the possible influence of a dose-adjusted systemic antithrombin III infusion (with a targeted antithrombin III plasma level of 120%) on a hypercoagulable state, as well as on acute thrombotic complications and late restenosis rate in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty. They found no significant differences in dose-adjusted antithrombin III infusion coagulation activation markers, for example prothrombin fragments F1+2, thrombin-α2 antithrombin complexes (TAT) and soluble fibrin. However, fibrin D-dimer plasma concentration was significantly reduced on days 3 and 4 in the antithrombin III-treated group. The authors considered these findings were the result of lower thrombin activation and therefore less secondary activation of the endogenous fibrinolytic system in antithrombin III-treated patients. There was no influence on acute outcome after percutaneous transluminal coronary angioplasty, including thrombotic occlusion, in the antithrombin III-treated group. The restenosis rate was not significantly lower in the antithrombin III-treated group, but a trend to a reduced restenosis incidence was seen. This may be because there was less coagulation activation in the antithrombin III-treated group.

Our understanding of the cellular and molecular mechanisms of restenosis remains limited. Restenosis is believed to result primarily from a 'response to injury' of the interventional trauma and from subsequent disturbed wound healing. Disproportional activation of one or more physiological wound-healing responses may result in poorly controlled and therefore persistent pathological reactivation, instead of self-limited and favourable vascular remodelling. These responses include platelet activation and aggregation, thrombin formation, cell recruitment and activation, cell proliferation, matrix synthesis and tissue contraction. At present no clear information is available about the definite role of thrombin formation in unstable patients with percutaneous transluminal coronary angioplasty and restenosis, although some hypothetical conclusions can be drawn and are worthy of discussion.

We cannot exclude the possibility that periprocedural thrombin formation is a prominent contributor to restenosis, even though no relationship has been found between an increase in direct (TAT, F1+2) and a decrease in indirect biochemical markers (D-Dimer) of thrombin activation and the development of late restenosis⁴⁵. These biochemical markers of thrombin generation are too sensitive to differentiate
between different extents of thrombin generation and exhibit an ‘acute phase’-like increase as a result of surgery or intracoronary interventions.

Thrombin has been shown to be one of the most potent triggers of restenosis, due to its stimulating effect on cell migration and proliferation via the thrombin receptor[6]. Platelet activation and aggregation, which are known to be responsible for early formation of platelet-rich thrombi after vessel trauma, are in part also stimulated by thrombin. Taken together, these explanations suggest a possible association between early thrombin generation and late restenosis after percutaneous transluminal coronary angioplasty. The study presented by Grip and co-workers[6] in this issue does not provide us with hard data to confirm this hypothetical relationship between thrombin activation and late restenosis. Like other authors, Grip et al.[6] were also unable to demonstrate a significant difference in levels of direct biochemical markers of thrombin activation (e.g. TAT complexes or F1+2 fragments) in patients with and without restenosis. Furthermore, no statistically significant effect of dose-adjusted antithrombin III treatment on restenosis could be demonstrated. However, patient numbers may have been too low to allow firm conclusions.

Just as prolonged antithrombotic therapy with heparin, coumadin, aspirin, dipyridamole and ticlopidine has failed to show a significant effect on restenosis, the addition of antithrombin III to heparin, coumadin, aspirin, dipyridamole and ticlopidine has failed to show a significant effect on restenosis. Like other authors, Grip et al.[6] were also unable to demonstrate a significant difference in levels of direct biochemical markers of thrombin activation (e.g. TAT complexes or F1+2 fragments) in patients with and without restenosis. Furthermore, no statistically significant effect of dose-adjusted antithrombin III treatment on restenosis could be demonstrated. However, patient numbers may have been too low to allow firm conclusions.

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Monoclonal antibodies against the glycoprotein IIb/IIIa receptor might, therefore, offer a more rational pharmacological approach for the prevention of procedure-related thrombus formation. The EPIC trial (Evaluation of 7E3 for the Prevention of Ischemic Complication), using the glycoprotein IIb/IIIa receptor antibody 7E3, has shown a reduction in early thrombosis-related cardiac events. This reduction was maintained, as demonstrated by long-term follow-up[8]. Whether the action of the IIb/IIIa receptor antibody 7E3 is caused exclusively by complete inhibition of platelet aggregation, whether it is due to interaction of 7E3 with the thrombin receptor on smooth muscle cells or due to alternative mechanisms, is currently under investigation. Future studies will have to concentrate on the development of agents directed specifically against the thrombin receptor, which is responsible for most thrombin-mediated mechanisms of restenosis. Such substances may also need to be applied as early as possible, preferably before initiation of trauma to the vessel.

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References