Drug eluting stents (DES) have been enthusiastically introduced into contemporary interventional cardiology practice. By delivering locally active doses of antiproliferative drugs, they have demonstrated an impressive capacity to inhibit restenosis caused by neointimal hyperplasia; a complication that has plagued uncoated “bare-metal” stents (BMS). DES coated with either paclitaxel or rapamycin (sirolimus) are now deployed in over 90% of coronary interventions in the United States. However, clinical follow-up has revealed significant concerns relating to the incidence of late (30 days) stent thrombosis, especially in long stents and after discontinuation of dual antiplatelet therapy.

Stent thrombosis with DES has been attributed to various potential mechanisms (Figure), but delayed or incomplete stent endothelialization has been proposed as a major mechanism. In a recent autopsy study, DES showed reduced endothelialization (27±26% versus 66±25%), especially in those with evidence of stent thrombosis. However, patients with DES had stents that were almost twice as long and included those receiving DES for indications not approved by the Food and Drug Administration, including acute myocardial infarction. This selected autopsy group represents the extreme end of the spectrum and may not reflect the situation in the majority of patients who receive DES and survive.

The hypothesis that late stent thrombosis is attributable solely to delayed endothelialization contrasts with porcine models of coronary stent implantation. Although endothelialization may be more rapid than in humans, endothelial coverage of DES and BMS in a porcine model is almost complete after 28 days with no significant difference between stents. Furthermore, the bulk of evidence now suggests that reendothelialization is achieved by blood-borne endothelial progenitor cells originating from the bone marrow. It is, therefore, hard to reconcile the hypothesis that locally active doses of antiproliferative agents impair reendothelialization by inhibiting the proliferation of adjacent endothelial cells.

With these observations in mind, Muldowney and colleagues in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, present a fascinating alternative and suggest a potential pathophysiological mechanism to explain the occurrence of late stent thrombosis in DES. Using microarrays of more than 11 500 genes, they report that, after incubation with either paclitaxel or rapamycin, the most consistent change in human endothelial gene expression was upregulation of the transcript for plasminogen activator inhibitor type 1 (PAI-1). They confirmed that these transcriptional effects were associated with increased PAI-1 antigen production. The upregulation of this antifibrinolytic factor presents an important potential mechanism underlying the prothrombotic effect of DES.

The fibrinolytic pathway describes a complex process involving the hydrolytic cleavage of fibrin, by plasmin, to cause clot dissolution. This process is regulated by a balance between the acute endothelial release of tissue plasminogen activator (t-PA) and its serpin inhibitor, PAI-1. Indeed, some have suggested that coronary thrombosis is particularly sensitive to imbalances in this fibrinolytic pathway. Animal models of PAI-1 overexpression exhibit spontaneous macrovascular coronary thrombosis and myocardial infarction. Plasma PAI-1 concentrations are independently predictive of adverse cardiovascular events in healthy populations and patients with coronary heart disease. Indeed, increased plasma PAI-1 concentrations are independently associated with major adverse cardiac events following BMS insertion, and autopsy observations have further indicated that persistent fibrin deposition is a risk factor for late stent thrombosis with DES.

Of further interest, Muldowney reports contrasting effects of paclitaxel and rapamycin on the expression and secretion of t-PA. Although rapamycin caused downregulation of t-PA mRNA expression and secretion, this effect was not seen in cells incubated with paclitaxel. Indeed, paclitaxel caused an increase in both expression and secretion in human umbilical vein endothelial cells. In the presence of impaired t-PA secretion, the prothrombotic effect of enhanced PAI-1 synthesis would be further amplified. Although other factors are likely to play a role, it is tempting to speculate that the combination of elevated PAI-1 and impaired t-PA secretion is a plausible explanation for the higher incidence of late stent thrombosis reported in one meta-analysis of patients treated with rapamycin-coated (Cypher, Cordis Corp) stents compared with paclitaxel-coated (Taxus, Boston Scientific Corp) stents.

Muldowney and colleagues extended their preliminary in vitro findings by examining the effects of rapamycin and paclitaxel delivered to transgenic mice expressing enhanced green fluorescent protein (eGFP) linked to the human PAI-1 promoter. After 2 weeks of intraperitoneal infusion, the expression of eGFP-linked PAI-1 promoter was increased in coronary arteries, aorta, and kidney from animals treated with these antiproliferative agents. Thus they were able to confirm the consistency of their in vitro findings using an in vivo approach.
model. Given that local PAI-1 expression is induced by percutaneous coronary intervention, the effects of rapamycin and paclitaxel would be anticipated to be enhanced even further at the site of stent implantation.

The dramatic reduction of in-stent restenosis associated with DES is an important therapeutic advance that has had a major impact on interventional cardiology. The small but significant absolute increase in late stent thrombosis is an important observation that remains a concern. Emerging mechanisms of DES thrombosis, including the induction of antifibrinolytic endothelial phenotypes, are helping us to understand this phenomenon. Such work will help inform the further refinement of this major therapeutic advance to allow physicians to have an effective and safe therapy for patients with obstructive atherosclerotic disease.

Disclosures

None.

References

Emerging Thrombotic Effects of Drug Eluting Stents
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