Uremic Serum and Ubiquitylation of Tissue Factor

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Stent thrombosis is a major clinical problem associated with a high rate of mortality.1,2 The development of drug-eluting stents has significantly reduced restenosis compared with bare metal stents as a result of the antiproliferative agents inhibiting vascular smooth muscle (VSMC) proliferation. However, the rate of stent thrombosis associated with drug-eluting stents continues to be a major concern, with rates between 0.3 and 1.1% within 3 years.3 Thrombosis is likely in part attributable to the fact that the antiproliferative drugs also inhibit re-endothelization of the vessel. Furthermore, patients with chronic renal failure have worse outcomes after stenting and have as much as an 8-fold increase in 1-year cardiac mortality after coronary intervention.3

Tissue factor (TF) is a transmembrane protein that triggers blood coagulation.4 It has been proposed that TF plays a role in stent thrombosis, although there is no direct evidence for this assumption in patients. Platelet binding to the damaged vessel with or without exposure of TF is equally likely to trigger thrombosis. In this issue of Circulation, Chitalia et al5 have made the interesting observation that uremic serum increases TF protein stability in VSMCs. They suggest that this may explain the increase in cardiac mortality in chronic renal failure patients receiving stents.

In healthy vessels, TF is separated from its ligand factor VIIa/VIIa in the blood by the endothelium, and this prevents inadvertent activation of blood coagulation. In the normal vessel wall, high levels of TF messenger RNA (mRNA) and protein are expressed by adventitial fibroblasts, where it provides hemostatic protection.6 TF mRNA and protein were below the detection limit in VSMCs, but 1 study found a low level of TF activity in normal rat aortic media.7 In animal models, endothelial denudation without medial injury is associated with platelet deposition without fibrin, whereas fibrin is observed with more severe injury that damages the media.8,9 These results suggest that exposure of adventitial TF is required for activation of blood coagulation and fibrin deposition. Surprisingly, deletion of the TF gene in VSMCs in mice reduced ferric chloride–induced thrombosis.10 This result suggests that VSMCs express low levels of functional TF that can induce thrombosis in some models.

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(Circulation. 2013;127:320-321.)
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Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.112.154666

The choice of VSMCs is relevant for studies in stent thrombosis. However, it should be noted that cultured human VSMCs express high basal TF expression compared with VSMCs in vivo. It would be interesting to examine TF
expression in the wall of stented vessels from patients with or without chronic renal failure. In addition, other cell types may express TF within the injured vessel wall, such as macrophages, and these could also contribute to stent thrombosis. The human VSMCs were studied in a flow-loop model that mimics coronary flow. Cells were exposed to control or uremic serum for 24 hours. No time-course experiments were presented, and the time points used to examine TF mRNA levels were not reported. One complication with the study is that serum is a strong inducer of TF expression in VSMCs. It is likely that the initial exposure of the cells to serum would transiently increase TF expression. Indeed, levels of TF protein and activity were higher in cells exposed to 10% uremic serum (3.3-fold) than TF activity (2-fold), whereas there was a similar increase (2-fold) of TF protein and activity in cells exposed to 5% uremic serum. This result suggests that TF protein is increasing without a corresponding increase in TF activity. Unfortunately, the method used to measure TF activity was not reported. Further, the TF activity of VSMCs exposed to 5 or 10% of control or uremic serum was not compared in the clot assay.

The triggers of stent thrombosis remain a mystery. What is particularly perplexing is that thrombosis can occur at a considerable time after deployment of the stent. Further studies are needed with animal models and patients to identify the sources of the prothrombotic material. Obviously, stents continue to be improved and increasing re-endothelization will reduce rates of thrombosis. At present, patients receiving stents are treated with platelet inhibitors to prevent thrombosis, but additional antithrombotic strategies may be beneficial in the future.

Disclosures

None.

References


Key Words: Editorials ■ stents ■ thrombosis
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_Circulation_. 2013;127:320-321; originally published online December 25, 2012;
doi: 10.1161/CIRCULATIONAHA.112.154666
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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