Thrombosis of Vein Grafts
Wall Tension Restrains Thrombomodulin Expression

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Thrombosis is a major complication leading to early vein graft failure in patients undergoing coronary artery bypass surgery. Like thrombosis at other sites, thrombosis of vein grafts results from a failure of hemostatic balance, which is normally maintained by a complex series of coagulation reactions that involve both systemic and local factors. The endothelium contributes to local hemostatic balance by producing thrombomodulin, which functions as an essential cofactor for the activation of anticoagulant protein C and other antithrombotic molecules such as heparin sulfates, plasminogen activators, and nitric oxide. The antithrombotic properties of endothelium may become compromised when vein grafts are exposed to the high-pressure arterial circulation.

As its name implies, thrombomodulin modulates the activity of thrombin from that of a procoagulant to an anticoagulant protease. When bound to thrombomodulin on the endothelial surface, thrombin is unable to generate fibrin or activate platelets but instead becomes a potent activator of protein C (see Figure). The activated form of protein C (APC) is an anticoagulant protease that selectively inactivates coagulation factors Va and VIIIa, providing an essential feedback mechanism to prevent excessive coagulation. Although activation of protein C in vivo is completely dependent on thrombomodulin, the efficiency of protein C activation is enhanced by another endothelial cofactor, the endothelial protein C receptor (EPCR). The clinical importance of the thrombomodulin/protein C anticoagulant pathway is underscored by the strong association between venous thromboembolism and resistance to APC caused by factor V Leiden.

In a recent article in Circulation Research, Rade and colleagues reported that endothelial expression of thrombomodulin, but not EPCR, decreased dramatically after autologous vein grafts were implanted into the carotid circulation of rabbits. The loss of thrombomodulin occurred rapidly, within two weeks of implantation, and was associated with an increase in bound thrombin activity. Reconstitution of thrombomodulin by adenovirus-mediated gene transfer prevented the increase in bound thrombin activity. A similar downregulation of thrombomodulin expression was observed in human saphenous vein segments placed under arterial flow conditions in an ex vivo perfusion system. Some loss of thrombomodulin activity may occur during harvesting of saphenous vein grafts, even before implantation in the arterial circulation.

Several potential mechanisms may contribute to loss of endothelial thrombomodulin activity in vein grafts. The decrease in thrombomodulin expression is temporally associated with a local inflammatory response, and transcription of the thrombomodulin gene is known to be negatively regulated by inflammatory cytokines such as tumor necrosis factor-α or interleukin-1β. The EPCR gene is also downregulated by inflammatory cytokines; therefore, preservation of EPCR in the face of decreased thrombomodulin suggests that inflammation-mediated transcriptional downregulation may not be a major mechanism for decreased thrombomodulin expression in vein grafts. An alternative possibility is that thrombomodulin may be shed from the endothelial surface by proteases produced by activated leukocytes. It is also possible that mechanical hemodynamic forces related to shear stress and/or pressure-induced vessel distension may alter thrombomodulin expression on vein grafts.

In the current issue of Circulation Research, Sperry et al describe new experiments in which a rabbit jugular vein implantation model was used to investigate the mechanisms by which thrombomodulin is lost from vein grafts. To address the role of inflammation, rabbits were treated with vinblastine to render them severely leukopenic. Surprisingly, the expression of thrombomodulin protein and mRNA in vein grafts did not differ between the control and leukopenic animals. This finding suggests that the decrease in thrombomodulin expression in vein grafts was not caused by inflammation-induced downregulation of thrombomodulin gene transcription or leukocyte-mediated shedding of thrombomodulin from the endothelial surface. Instead, Sperry et al found that hemodynamic forces play a key role in regulating thrombomodulin expression in vein grafts. By comparing the effects of rigid external stents (which prevented distension of the vessel wall) with surgical manipulations that either decreased or increased blood flow, they demonstrate that wall tension is a major negative regulator of thrombomodulin expression. Interestingly, the level of expression of thrombomodulin was independent of blood flow or shear stress.

The findings of Sperry et al implicate pressure-induced changes in vessel wall tension, with concomitant endothelial deformation (strain), as a major regulator of thrombomodulin expression in vivo. This conclusion is somewhat discrepant from that of Gosling et al, who found that external stenting did not prevent the decrease in thrombomodulin expression that occurs within 90 minutes when human saphenous veins are exposed to arterial flow conditions in an ex vivo perfusion circuit. Additional studies will be needed to determine whether the discrepant results from these two studies are related to the use of different types of stents, the different time courses of the experiments, or
Local activation of coagulation reactions in vein grafts may lead to generation of thrombin. When thrombomodulin (TM) is lost from the endothelial surface, thrombin promotes thrombosis by activating platelets and cleaving fibrinogen to form fibrin clots. When bound to TM on the endothelial surface, thrombin is unable to cleave fibrinogen or activate platelets, but instead serves as a cell-bound activator of protein C. Activation of protein C is further enhanced by the endothelial protein C receptor (EPCR). Activated protein C (APC) functions as a feedback inhibitor of thrombin generation and also has potent antiinflammatory properties.

Regardless of whether inhibition of thrombomodulin expression is triggered primarily by endothelial deformation or other effects of high-pressure pulsatile blood flow, the experiments performed by Sperry et al.\(^4\) provide strong support for the hypothesis that mechanical forces play an important role in the regulation of hemostatic balance in vivo. Endothelial expression of thrombomodulin is known to vary dramatically in different vascular beds, and it is likely that differences in wall tension contribute to this variability. Changes in wall tension also may contribute to altered thrombomodulin expression in atherosclerotic arteries. Expression of thrombomodulin is decreased in endothelium overlying human atherosclerotic plaques,\(^5\) and activation of protein C in response to infusion of thrombin is impaired in atherosclerotic primates.\(^6,7\) Vascular remodeling of atherosclerotic arteries, with attendant changes in wall tension and distensibility, may explain some of these observations.

Is decreased thrombomodulin expression a major factor leading to vein graft thrombosis in patients undergoing bypass surgery? Although the work of Sperry et al.\(^4\) clearly advances our understanding of the factors responsible for regulating thrombomodulin expression in vivo, a direct role for the thrombomodulin/protein C anticoagulant pathway in preventing vein graft thrombosis has not been established. If thrombomodulin does protect from vein graft failure, it could do so by inhibiting thrombin’s procoagulant activities, decreasing local generation of thrombin, and increasing production of APC, which has potent antiinflammatory as well as antithrombotic properties (see Figure).\(^10\) Local overexpression of thrombomodulin through adenoviral gene transfer has been shown to prevent thrombosis in an animal model.\(^18\) It remains to be seen, however, whether gene therapy approaches will prove to be a viable clinical strategy for preventing thrombosis of vein grafts. Alternative therapeutic strategies might include the use of external stents\(^19\) or pharmacological approaches such as oral direct thrombin inhibitors\(^20\) or infusion of APC, which is now approved for use in patients with bacterial sepsis and disseminated intravascular coagulation.\(^10\)

**References**


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