Thoracic and Cardiovascular Surgery

Antithrombotic Controversies in Off-Pump Coronary Bypass

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The purpose of this article is to evaluate the use of perioperative antithrombotics in patients undergoing surgical revascularization of the coronary vessels. Although there is a general agreement about the use of anticoagulation during off-pump coronary revascularization (OPCAB), the degree of the required anticoagulation varies from one center to another. The review is divided into four major sections. The first section describes the pathophysiology of the coagulation system in cardiac surgery with and without the use of cardiopulmonary bypass. In this section, we also discuss the interactions between the coagulation system and the inflammatory response to cardiac surgery. The second section examines the role of prophylactic antithrombosis in patients referred to surgical revascularization, and their role in bleeding complications associated with surgery. Heparinization and neutralizing its anticoagulative effects during coronary surgery are discussed in the third section. The fourth section examines the evidence that the inflammatory response contributes to adverse peri-operative events, in particular organ dysfunction, and potential therapeutic strategies to control this response. The review concludes with a summary of potential future research directions and key deficiencies in our knowledge regarding the use of anticoagulants in cardiac surgery.
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Coronary vascular disease and resulting myocardial ischemia is the leading cause of death in the aging populations of developed countries. While there is a decrease in the oxygen supply to the heart, a considerable portion of the myocardium is still viable and may resume its function on reperfusion. The terms "stunned" and "hibernating" myocardium generally refer to the reversible loss of contractile function of the heart. Coronary revascularization is an important therapeutic measure that is offered for the patient with advanced atherosclerotic lesions involving myocardial circulation. Recent advances in the field of interventional cardiology and introduction of medicated stents have resulted in a shift of high risk patients for surgical revascularization.

Coronary vascular surgery has evolved remarkably since its early introduction to minimize the risk and postoperative complications. Although early reperfusion of ischemic myocardium is critical and life-saving, coronary artery bypass grafting (CABG) is associated with intraoperative and early postoperative complications such as surgical bleeding, stroke, and perioperative myocardial infarction. The use of cardiopulmonary bypass (CPB) has been cited to be responsible for some of these complications such as cerebrovascular events observed following CABG. Although avoiding CPB during coronary revascularization has significantly decreased some of these neurological and bleeding complications, a significant number of the patients still suffer from thromboembolic events, or a postoperative bleeding diathesis.

Pathophysiology of Coagulation System During Cardiac Surgery

Normal hemostasis is a fine balance between the endogenous anticoagulants and procoagulants. Endogenous anticoagu-

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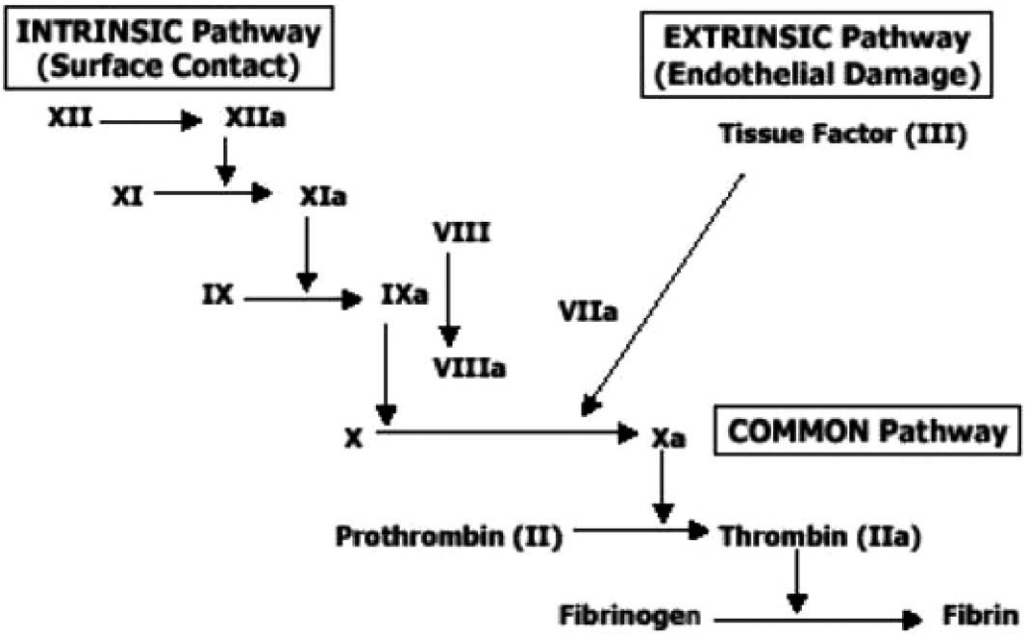

Figure 1 Activation of coagulation system.

lant activity slightly overcomes the procoagulant activity which is necessary for the continuous intravascular flow of blood. The smooth surface of the endothelium contributes to the endogenous activation of the coagulation system.[1] Any damage to this surface results in a process that leads to the occlusion of the affected vessel.[2] A more subtle type of this vascular injury is the cornerstone of the atherogensis, where the vascular endothelium is damaged by activation of microsomal enzymes.[3] Any insult to the integrity of the vascular bed such as those during surgery initiates a series of enzymatic activation that decreases the natural dominance of anticoagulant system versus procoagulant system.

This loss of balance between endogenous anticoagulant and coagulation system is known as hemostasis and is a defense mechanism to prevent life-threatening blood loss during surgery. The coagulation system consists of multiple serine protease proenzymes that become enzymatically active on a proteolytic cleavage by another enzyme (Fig. 1). The cascade of enzymatic activation may either be initiated intrinsically or as a result of an exogenous injury to the vascular endothelium (extrinsic pathway). Regardless of the source, the final steps of coagulation are completed by activation of the common pathway.

Once the endothelial bed is injured, the released tissue factors serve as potent activators of platelets and facilitate their adherence to the vascular wall.[2] The aggregated platelets become the primary nidus of the future thrombus.[4,5] Adhesion of platelets to the endothelial bed is mediated through the surface proteins that are produced and stored in platelets and endothelial cells such as Von Willebrand factor (vWF).[5] High molecular weight kininogen (HK) and zinc stimulate the expression of vWF on the surface of both platelets and endothelial cells. However, only activated platelets expressing this factor are able to bind to coagulation factor XI and consolidation of the plug.[6] In the resting state, GP IIb/IIIa binds only to fibrinogen molecules attached to a solid substrate, such as the extracellular matrix. However, on platelet activation, GP IIb/IIIa appears to undergo a conformational change and becomes able to bind several extracellular matrix proteins, among which fibrinogen plays a principal role.[7] Adhesion of platelets to each other is further enhanced by the release of adenosine di-phosphate (ADP) and further consolidation of preliminary loose plug. Additionally, the release of coagulation factor XIII mediates the firmer adhesion of the platelets to the endothelial cells through platelet glycoproteins, which can be effectively inhibited by a specific antibody against GPIIb/IIIa, Abciximab.[8]

Activation of platelets has been identified as a major contributor to the hypercoagulable state during OPCAB by several studies. A recent study by Gerrah and coworkers has demonstrated an increase in platelet adhesion and aggregation to the plate using cone and plate technology in a small group of patients undergoing OPCAB.[9] This group has shown that both average size (AS) and surface covered (SC) increase approximately 30% following OPCAB. A limited multivariate and univariate analysis of the data obtained from this work has shown a direct relation between preoperative platelet dysfunction and the amount of postoperative bleeding. There was no significant relation between the preoperative number of platelets and postoperative bleeding in three patients despite a trend that may have been significant if a larger number of patients were tested. Although the overall values of these parameters do not reach a clinically significant thrombogenic state in this study, this level of increase may be clinically alarming for increasing incidence of thrombotic events after OPCAB. The most important finding of this investigation is probably the fact that it increases our awareness toward considering platelets as therapeutic targets to minimize thrombotic complications following coronary revascularization.

Coagulation and inflammation share several common proteins and mediators. Examination of the microcirculatory